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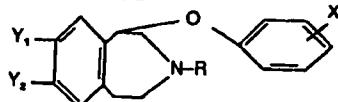
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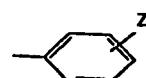
⑯ 1-Aryloxy-2,3,4,5-tetrahydro-3-benzazepines, a process for preparing the same and their use as medicaments.

⑯ The invention relates to 1-aryloxy-2,3,4,5-tetrahydro-3-benzazepines of the formula

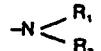


wherein Y₁ and Y₂ are the same or different and are hydrogen or lower alkoxy; X is hydrogen, halogen, lower alkyl, lower alkoxy, CF₃, NO₂, CN and NH₂; R is hydrogen, lower alkyl, cycloalkyl or lower alkyl.

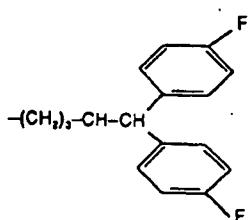
Ar lower alkyl of the formula -alkylene



where Z is hydrogen, lower alkyl, lower alkoxy, halogen, CF₃, NO₂ and NH₂; and an alkylene amine of the formula -alkylene



where R₁ and R₂ are the same or different and are hydrogen and lower alkyl and the alkylene moiety is of 1 to 6 carbon atoms, and the pharmaceutically acceptable acid addition salts thereof.



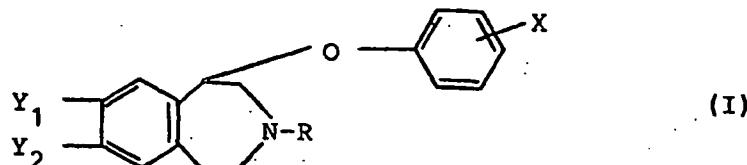
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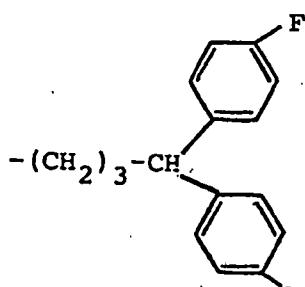
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To the best of our knowledge the compounds of the present invention have not heretofore been described or suggested.

The compounds of the present invention have the
5 general formula



10 wherein Y_1 and Y_2 are the same or different and are hydrogen or lower alkoxy; X is hydrogen, halogen, lower alkyl, lower alkoxy, CF_3 , CN , NO_2 or NH_2 ; R is hydrogen, lower alkyl, cycloalkyl lower alkyl.



Ar lower alkyl of the formula -alkylene  , where Z is hydrogen, halogen, lower alkyl, lower alkoxy, CF_3 , NO_2 and NH_2 ; and an alkylene amine of the formula -alkylene- $\text{N}^<_{\text{R}_2}^{\text{R}_1}$, where R_1 and R_2 are the same or different and are hydrogen or lower alkyl; and the pharmaceutically acceptable acid addition salts thereof.

In the above definitions the term "lower" means the group it is describing contains from 1 to 6 carbon atoms. The term "alkyl" refers to a straight or branched chain hydrocarbon containing no unsaturation, e.g. methyl, ethyl, isopropyl, 2-butyl, neopentyl, n-hexyl, etc; the term "alkoxy" refers to a monovalent substituent which consists of an alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen, e.g. methoxy, ethoxy, propoxy, butoxy, pentoxy, etc.; the term "cycloalkyl lower alkyl" refers to

a monovalent substituent consisting of a saturated hydro-carbon group possessing at least one carbocyclic ring, of 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc., linked

5 through a lower alkyl group having its free valence bond from a carbon of the lower alkyl group; the term "Ar lower alkyl" refers to a monovalent substituent which consists of an aryl group, e.g., phenyl, p-nitro phenyl, o-tolyl, m-methoxy phenyl, etc. linked through

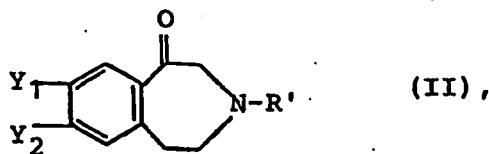
10 a lower alkylene group having its free valence bond from a carbon of the lower alkylene group, and having a formula of -alkylene-Z, where the Z is hydrogen, halogen, lower alkyl, lower alkoxy, CF₃, NO₂ and NH₂; the term "alkylene" refers to a bivalent radical of the lower

15 branched or unbranched alkyl group it is derived from having valence bonds from two terminal carbons thereof, e.g. ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-) iso-propylene (CH₃-CH-CH₂-), etc.; and the term "halogen" refers to a member of the family consisting of fluorine,

20 chlorine, bromine and iodine.

The compounds of the present invention are prepared in the following manner. The substituents Y₁, Y₂, X, R, R₁ and R₂ are as defined above unless indicated otherwise. A substituted benzazepine of the formula

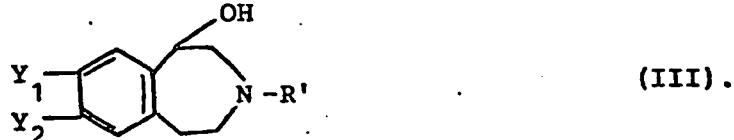
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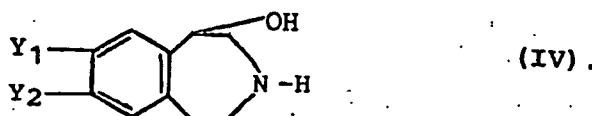
where R' is the tosyl group (-SO₂--CH₃) or the mesyl group (-SO₂CH₃), is selected. Compound II is reduced in a conventional manner, for example by reaction with NaBH₄, to form a substituted 1-hydroxy-2,3,4,5-tetrahydro-3-benzazepine of the formula

35



Compound III is detosylated or demesylation by means of reduction with an alkali metal such as Na° or K° , in liquid ammonia or ethanol, or by reduction with a complex boron or aluminiumhydride e.g. sodium bis(2-methoxyethoxy) aluminium hydride etc., to form a 1-hydroxy-2,3,4,5-tetrahydro-3-benzazepine of the formula

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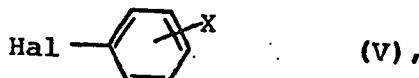


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The preparation of compound II, its reduction to compound III and the detosylation or demesylation of compound III to yield compound IV are well known and are easily arrived at by one skilled in the art from the prior art such as M.A. Rehman, et al., J. Chem. Soc. (C) 58 (1967) and G. Hazebroucq, Ann. Chim., I, 221 to 254 (1966), both of which are incorporated by reference hereinto.

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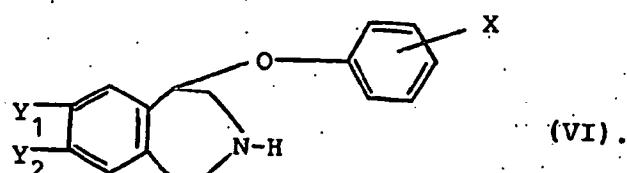
Compound IV is reacted with a halide having the formula



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where X is as previously defined, and Hal is halogen to form a compound of the invention

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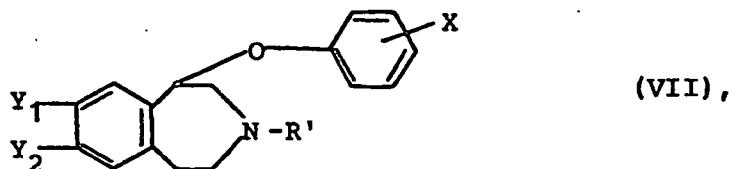


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Compound VI is typically obtained by reacting compounds IV and V under nucleophilic reaction conditions, such as those of the conventional Williamson ether synthesis, as for example in the presence of a strong base, e.g. NaH , and an inert solvent, e.g., dimethylformamide (DMF), dimethylsulfoxide (DMSO), benzene, toluene, and a temperature of 0° to 120°C for 2 to 96 hours.

Compound VI can also be prepared in the following manner. Compound III is reacted with halide V in the manner described above to form an intermediate of the invention having the formula

5



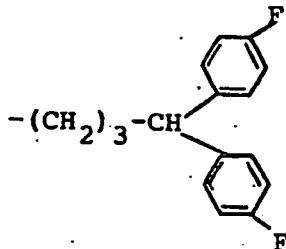
10 where R' is tosyl or mesyl. Compound VII is then reacted under conventional conditions with the well-known reducing agent sodium bis(2-methoxyethoxy)aluminium hydride, $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$, e.g. in an inert solvent, such as toluene, at a temperature of 25 to 70°C for 15 24 to 28 hours, to detosylate or demesylate compound VII to form compound VI. In an alternative manner, compound III is reacted with a phenol of the formula

20

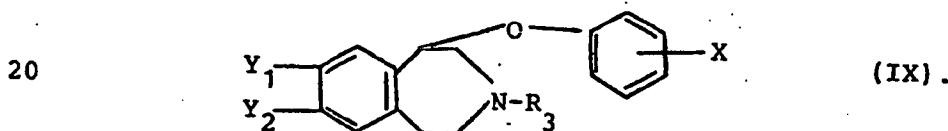


in the manner described in U.S. Patent 4,216,218. That is, compound III and compound IV are combined with triphenylphosphine and a solvent, e.g., benzene. Diethylazodicarboxylate is then added to the resultant 25 solution. The resultant reaction mixture is maintained under a nitrogen atmosphere at a temperature of 5 to 25°C, typically for 6 to 30 hours to form intermediate compound VII which in turn is then reacted with the sodium bis(2-methoxy-ethoxy)aluminum hydride to form compound VI of 30 the invention.

Compound VI of the invention is reacted under conventional nucleophilic reaction conditions with a halide having the formula Hal-R_3 , where Hal is halogen and R_3 is lower alkyl; cycloalkyl lower alkyl;



alkylene $-\text{C}=\text{C}^{\text{Z}}$ where the alkylene moiety is of 1 to 6 carbon atoms and Z is hydrogen, halogen, lower alkyl, lower alkoxy, CF_3 , NO_2 or NH_2 ; $-\text{C}^{\text{O}}-\text{R}_4$ where R_4 is alkyl of 10 1 to 5 carbon atoms or $-\text{alkylene}-\text{C}=\text{C}^{\text{Z}}$, where the alkylene moiety is of 1 to 5 carbon atoms and Z is as defined above; $-\text{alkylene}-\text{CN}$ where the alkylene moiety is of 1 to 5 carbon atoms; $-\text{alkylene}-\text{N}^{\text{R}_1}-\text{R}_2$, where the alkylene moiety is of 1 to 6 carbon atoms; and $-\text{alkylene}-\text{C}^{\text{O}}-\text{NH}_2$ 15 where the alkylene moiety is of 1 to 5 carbon atoms, to form a compound of the invention



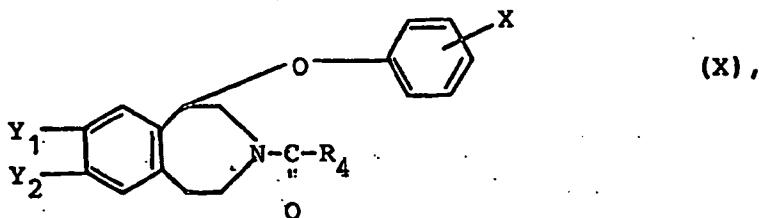
(IX).

Typically, compound VI is reacted with a halide $\text{Hal}-\text{R}_3$ in the presence of a base, e.g., NaHCO_3 , K_2CO_3 , Na_2CO_3 , etc. and an inert solvent, e.g. DMF, butanol, acetone, 2-butanone, etc., at a temperature of 70 to 120°C for 2 to 24 hours, to form compound VIII. Where R_3 is lower alkyl or Ar lower alkyl of the formula $-\text{alkylene}-\text{C}=\text{C}^{\text{Z}}$, typically this reaction is carried out in the presence of K_2CO_3 or Na_2CO_3 , at a temperature of 70 to 120°C for 2 to 24 hours to form compound IX where R_3 is lower alkyl or $-\text{alkylene}-\text{C}=\text{C}^{\text{Z}}$ (Ar lower alkyl).

When R_3 of the halide $\text{Hal}-\text{R}_3$ is $-\text{C}^{\text{O}}-\text{R}_4$, typically the reaction is run in the presence of a base such as NaHCO_3 , triethylamine, etc., a solvent such as CH_2Cl_2 , CHCl_3 , etc., at a temperature ranging from 5 to 60°C for 2 to 24 hours to produce a compound.

IX where R_3 is $-\overset{O}{\underset{||}{C}}-R_4$ which is an intermediate of the invention having the formula

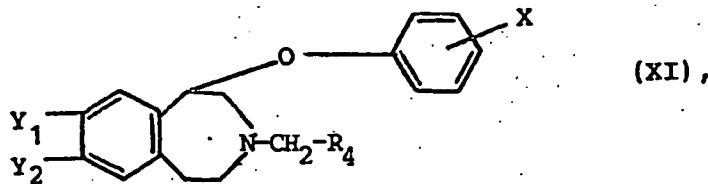
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10 where R_4 is as previously defined. The carbonyl group of compound X is reduced to a methylene group in a conventional manner with such reducing agents as complex metal hydrides, e.g., $LiAlH_4$, sodium bis(2-methoxyethoxy)aluminum hydride, etc. to form a compound of IX of the invention where R_3 is lower alkyl or Ar lower alkyl having the

15 formula

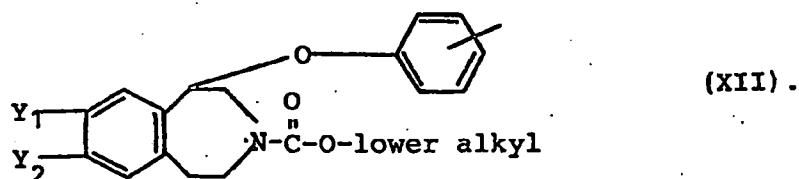
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where R_4 is as defined above.

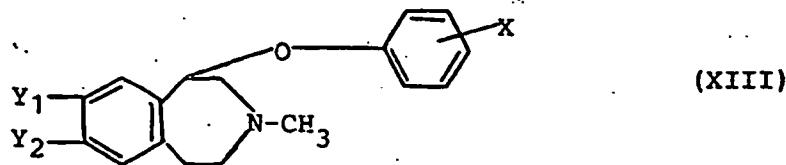
25 In an alternative procedure to produce compound VIII where R_3 is methyl, compound V is reacted in a conventional manner with a lower alkyl haloformate, e.g. ethylchloroformate, to form an intermediate of the invention

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Compound XII can then be reduced in a conventional manner, such as by treatment with $LiAlH_4$, etc. to form compound XIII where R_3 is methyl,

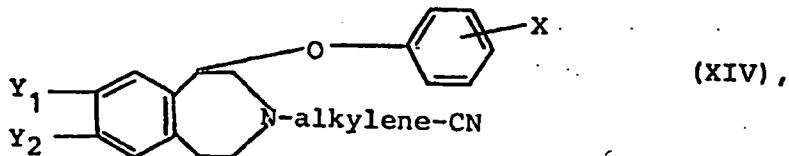
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Where the halide Hal-R₃ is a halo substituted alkyl nitrile, e.g. chloroacetonitrile, the halide is reacted with compound VI in the presence of a base, e.g. NaHCO₃, K₂CO₃, etc., in a suitable solvent, e.g. DMF etc., at a temperature of 25 to 60°C for 1 to 3 hours to form compound IX where R₃ is -alkylene-CN, that is an intermediate compound of the invention having the formula

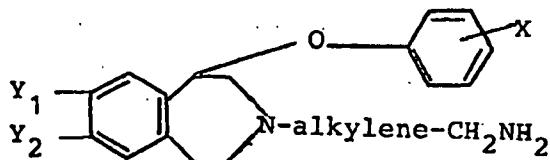
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where the alkylene moiety is of 1 to 5 carbon atoms.

Compound XIV in turn is reduced by conventional means, e.g. with a metal hydride such as LiAlH₄, sodium bis(2-methoxyethoxy)-aluminum hydride or borane, etc. in an inert solvent such as THF etc., at a temperature of 25 to 65°C for 1 to 3 hours to reduce the cyano group to form a compound of the invention

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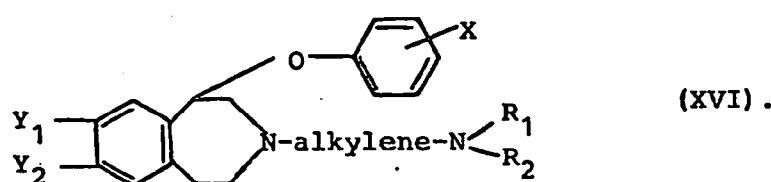
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where the alkylene moiety is of 1 to 5 carbon atoms, (XV).

Where the halide Hal-R₃ is a halo substituted alkylamine (N-substituted or unsubstituted), the halide Hal-R₃ and compound VI are typically reacted in the presence of a base, e.g. Na₂CO₃, K₂CO₃, etc., and a solvent, e.g. DMF, n-butanol, etc., at a temperature of 25 to 80°C for 1 to 3 hours to form compound IX of the

invention where R_3 is -alkylene-N $\begin{array}{c} R_1 \\ | \\ R_2 \end{array}$, where the alkylene moiety is of 1 to 6 carbon atoms,

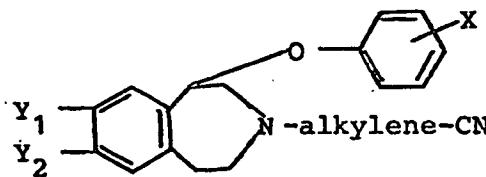
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(XVI).

In an alternative embodiment, compound VI is reacted
10 with a branched or straight chained alkenyl cyanide having
a formula Alkenyl-CN where the Alkenyl moiety is 1 to 5
carbon atoms, e.g. acrylonitrile, typically at a tempera-
ture of 25 to 80°C for 1 to 20 hours to form the inter-
mediate compound of the invention whereby there is addition
15 across the unsaturated bond to form the intermediate
compound of the invention having the formula

20



where the alkylene moiety has 1 to 5 carbon atoms, (XIV).

The intermediate XIV is reduced, as described above,
to form the compound of the invention having the formula
25 (XV).

The N-alkyl derivatives of compounds XV and XIII,
and compound XVI where R_1 and/or R_2 is hydrogen, are
prepared in a conventional manner, as for example by
reaction with an alkyl halide compound whereby a mono-
30 or bi-substituted compound is obtained, where at least R_1
or R_2 is lower alkyl. Alternatively these compounds can
be reacted with an alkyl or aryl chloroformate followed
by reduction of the resultant compound, as with LiAlH_4 ,
or sodium bis(2-methoxyethoxy)aluminum hydride, to form
35 a compound of the invention where at least R_1 or R_2 is
methyl.

It is understood that when X and/or Z is nitro that such group can be reduced to amino using conventional reducing agents and conditions, e.g. treatment with a metal and acid; catalytically with hydrogen and Pt, Pd, etc.; or a metal hydride, such as LiAlH₄.

The utility of the compounds of the present invention in the treatment of depression in mammals is demonstrated by their ability to inhibit tetrabenazine induced ptosis in mice (International Journal of Neuropharmacology 8, 73 (1969)), a standard assay for useful antidepressant properties. The antidepressant activities of some of the compounds of the invention expressed in terms of a 50 % inhibition of ptosis of tetrabenazine-induced ptosis in mice is given in Table I.

15 Table 1

	Compound	ED ₅₀ (oral) (mg/kg of body weight)	ED ₅₀ (intra-peritoneal) (mg/kg of body weight)
20	7,8-dimethoxy-3-methyl-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine oxalate	3.8	-
25	7,8-dimethoxy-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine oxalate	3.7	0.85
30	3-(2-aminoethyl)-1-(3-chlorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine dioxalate	7.5	-
35	1-(3-chlorophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine oxalate	4.2	1.1
	1-(4-trifluoromethylphenoxy)-2,3,4,5-tetrahydro-3-benzazepine oxalate	-	2.9
35	imipramine	-	1.28

These data indicate that the compounds of the present invention would be useful as antidepressants in mammals when administered in amounts ranging from 0.1 to 50 mg/kg of body weight per day.

5 The compounds of the invention are also useful as antihypertensive agents due to their ability to depress blood pressure in mammals. Antihypertensive activity is measured in the spontaneous hypertensive rat by the indirect tail cuff method described in "Methods in
10 Pharmacology," A. Schwartz, Ed., Vol. I, Appleton-Century Crofts, New York, 1971, p. 135. In this procedure a group of five animals are treated orally for three days with the test compound in relation to the control group of the same number. The drop in blood pressure is measured on the
15 third day following administration. The antihypertensive activities of some of the compounds, expressed as mm decrease in mean arterial blood pressure are given in Table II.

Table II

	Compound	Dose mg/kg of body weight	Decrease in Blood Pressure mm Hg
20	3-methyl-1-(4-methyl-phenoxy)-2,3,4,5-tetrahydro-3-benzazepine hydrobromide	50	35
25	1-(4-methoxyphenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine hydrobromide	50	48
30	3-(2-amino-1-methyl)ethyl-2,3,4,5-tetrahydro-1-(4-trifluoromethylphenoxy)-3-benzazepine dioxalate	50	51
	3-(2-methylaminoethyl)-2,3,4,5-tetrahydro-1-(4-trifluoromethylphenoxy)-3-benzazepine dioxalate	50	33

Table II

	Compound	Dose mg/kg of body weight	Decrease in Blood Pressure mm Hg
5	7,8-dimethoxy-3-methyl 2,3,4,5-tetrahydro-1-(4-tri- fluoromethylphenoxy)-3- benzazepine hydrochloride	50	43
10	7,8-dimethoxy-2,3,4,5- tetrahydro-1-(4-trifluoro- methylphenoxy)-3-benzazepine oxalate	50	49
	3-(2-aminoethyl)-2,3,4,5- tetrahydro-1-(4-trifluoro- methylphenoxy)-3-benzazepine dioxalate	50	61
15	guanethidine	50	20

Blood pressure reduction is achieved when the compounds of the invention are administered to a subject requiring such treatment at an effective oral, parenteral or intravenous dose of from 0.1 to 50 mg/kg of body weight per day. A preferred effective dose within this range is from about 0.1 to 5 mg/kg of body weight per day. A particularly preferred effective amount is about 1 mg/kg of body weight per day. It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted according to the individual need and the professional judgment of the person administering or supervising the administration of the compounds of the invention. It is to be further understood that the dosages set forth herein are examples only and that they do not, to any extent, limit the scope or practice of the invention.

The compounds of the invention are also useful as analgesic agents due to their ability to alleviate pain in mammals. The activity of the compound is demonstrated in the 2-phenyl-1,4-benzoquinone-induced writhing test in mice, a standard assay for analgesia (Proc. Soc. Exptl. Biol. Med., 95, 729 (1957)). The analgesic activity of some of

the compounds expressed in terms of percent inhibition of writhing are given in Table III.

Table III

		Dose (subcutaneous) mg/kg of Body Weight	Inhibition of Writhing %
5	Compound		
7,8-dimethoxy-1-(4-methoxyphenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine hydrochloride	7.6	50	
10	7,8-dimethoxy-3-methyl-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine oxalate	20	58
	1-(4-methoxyphenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine hydrobromide	25	46
15	3-(3-aminopropyl)-2,3,4,5-tetrahydro-1-(4-trifluoromethylphenoxy)-3-benzazepine dimaleate	8.2	50
20	1-(3-chlorophenoxy)-3-(2-phenylethyl)-2,3,4,5-tetrahydro-3-benzazepine oxalate	25	42
	1-(3-chlorophenoxy)-3-cyclopropylmethyl-2,3,4,5-tetrahydro-3-benzazepine oxalate	25	66
25	7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-1-(4-trifluoromethylphenoxy)-3-benzazepine hydrochloride	5.7	50
	propoxyphene	3.9	50

30 The analgesic relief of pain is achieved when the compounds of the invention are administered to a subject requiring such treatment at an effective oral, parenteral or intravenous dose of from 0.1 to 25 mg/kg of body weight per day. A preferred effective dose within this range is
35 from about 1 to 10 mg/kg of body weight per day. A particularly preferred effective amount is about 2 mg/kg

ob body weight per day. It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted according to the individual need. It is further to be understood that the dosages set forth 5 herein are examples only and that they do not, to any extent limit the scope of practice of the invention.

Effective amounts of the compounds of the present invention may be administered to a subject by one of various methods, for example, orally as in capsules or 10 tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The compounds of the invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition 15 salts for purposes of stability, convenience of crystallization, increased solubility and the like.

Preferred pharmaceutically acceptable acid addition salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, 20 perchloric acids and the like as well as organic acids such as tartaric, citric, acetic, succinic, maleic, fumaric acids and the like.

The compounds of the present invention may be administered orally, for example, with an inert diluent or 25 with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, 30 wafers, chewing gums and the like. These preparations should contain at least 4 % of the 1-aryloxy-2,3,4,5-tetrahydro-3-benzazepine of the invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4 % to about 70 % of 35 the weight of the unit. The amount of the compound present in such compositions is such that a suitable dosage will

be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 5.0-300 milligrams of the 1-aryloxy-2,3,4,5-tetrahydro-3-benzazepines of the 5 invention.

The tablets, pills, capsules, troches and the like may also contain the following adjuvants: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent 10 such as alginic acid, Primogel, corn starch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate or 15 orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. 20 Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various 25 compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the compounds of the present invention may be incorporated into a solution or suspension. These preparations 30 should contain at least 0.1 % of the 1-aryloxy-2,3,4,5-tetrahydro-3-benzazepines of the invention, but may be varied to be between 0.1 and about 50 % of the weight thereof. The amount of the inventive compound present in such compositions is such that a suitable 35 dosage will be obtained. Preferred compositions and preparations according to the present invention are

prepared so that a parenteral dosage unit contains between 5.0 to 100 milligrams of the 1-aryloxy-2,3,4,5-tetrahydro-3-benzazepines of the invention.

The solutions or suspensions may also include the following adjuvants: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diamine-tetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Other compounds of the invention include:

7,8-dimethoxy-1-(4-fluorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine;
7,8-dimethoxy-1-(4-fluorophenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine;
1-(4-chlorophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine;
1-(4-chlorophenoxy)-7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-3-benzazepine;
1-(3,4-dichlorophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine;
1-(3,4-dichlorophenoxy)-7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-3-benzazepine;
1-(4-bromophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine;
1-(4-bromophenoxy)-7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-3-benzazepine;
7,8-dimethoxy-1-(2-fluorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine;

7,8-dimethoxy-1-(2-fluorophenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine;
1-(2-chlorophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine;
5 1-(2-chlorophenoxy)-7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-3-benzazepine;
7,8-dimethoxy-1-phenoxy-3-(n-propyl)-2,3,4,5-tetrahydro-3-benzazepine; and
10 7,8-dimethoxy-3-ethyl-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine.

The following examples are for illustrative purposes and are not to be construed as limiting the invention disclosed herein. All temperatures are given in degrees centigrade.

15 Example 1

1-(p-Trifluoromethylphenoxy)-2,3,4,5-tetrahydro-3-benzazepine oxalate

A solution of 1-hydroxy-2,3,4,5-tetrahydro-3-benzazepine (9.78 g; 0.06 mole) in dimethylformamide (DMF) (150 ml) was added at room temperature to a suspension of sodium hydride (3.1 g. 50 % (98 %) oil dispersion, 0.063 mole, washed twice with hexane) in DMF (75 ml). The mixture was stirred at room temperature for one hour, and a solution of p-fluorobenzotrifluoride (10.35 g, 0.063 mole) in DMF (60 ml) was added. This mixture was stirred at room temperature about 16 hours overnight. The reaction was warmed at 70°C for one hour then stirred at room temperature overnight again. The mixture was poured into an ice/water mixture and extracted with dichloromethane; the dichloromethane extract was washed four times with water then once with saturated sodium chloride, then treated with charcoal, filtered through Celite-MgSO₄, and dried over MgSO₄. Removal of the solvent yielded 14 g. of an oil (76 %). A solution of oxalic acid in ether was added to a solution of 4 g of the oil in ether to give 3 g of product. Recrystallization from ethyl

acetate-methanol yielded 2 g of 1-(p-trifluoromethyl-phenoxy)-2,3,4,5-tetrahydro-3-benzazepine oxalate m.p. 208-209°C.

Analysis:

5 Calculated for $C_{17}H_{16}F_3NO.(CO_2H)_2$: 57.42% C 4.57% H 3.52% N
Found: 57.32% C 4.40% H 3.34% N

Example 2

1-(p-Chlorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine oxalate

10 A solution of 1-hydroxy-2,3,4,5-tetrahydro-3-benzazepine (14.3 g, 0.088 mole) in DMF (190 ml) was added at room temperature to a suspension of sodium hydride (4.9 g, 50% (98%) oil dispersion, 0.010 mole, washed twice with hexane) in DMF (50 ml). The mixture was
15 stirred at room temperature for one hour, warmed to 65°C for one hour, then cooled again to room temperature. A solution of 4-fluorochlorobenzene (13.8 g; 0.11 mole) in DMF (40 ml) was added. The mixture was stirred at room temperature overnight (about 16 hours), then was warmed at
20 75°C for six hours. The solvent was removed in vacuo to yield an oil which was stirred with water, then extracted with dichloromethane. The organic extracts were washed twice with water then dried (saturated NaCl, anhydrous $MgSO_4$). The solution was filtered and then concentrated to
25 an oil (20 g) which was dissolved in ether then converted to the oxalate salt as in Example 1 (6 g, 19%, m.p. 80-90°C). This material was twice recrystallized from ethyl acetate/methanol to yield 1-(p-chlorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine oxalate, d 198-199.5°C.

30 Analysis:

Calculated for $C_{16}H_{16}ClNO.(CO_2H)_2$: 59.42% C 4.99% H 3.85% N
Found: 59.25% C 5.20% H 4.05% N

E x a m p l e 3

1-(p-Nitrophenoxy)-2,3,4,5-tetrahydro-3-benzazepine
hydrochloride

A solution of 1-hydroxy-2,3,4,5-tetrahydro-3-benz-
5 azepine (7.5 g, 0.046 mole) in DMF (90 ml) was added at
room temperature to a suspension of sodium hydride (2.7 g.
50 % (98%) oil dispersion, 0.055 mole, washed twice with
hexane) in DMF (25 ml). The mixture was warmed to 50°C for
one hour, then cooled to 0-5°C then a solution of 1-fluoro-
10 4-nitrobenzene (7.5 g. 0.053 mole) in DMF (10 ml) was
added. The mixture was stirred at room temperature for
four hours. The solvent was removed to yield an oil which
was stirred with water, then extracted with chloroform. The
organic extracts were washed twice with water then dried
15 (saturated NaCl, anhydrous MgSO₄). The solution was filtered,
then concentrated to an oil (14 g) which was dissolved in
hot methanol/ether. The oil was then converted to the
hydrochloride salt (5.5 g of a solid, 37 %, 218-220°C)
by the addition of ethereal-HCl. This material was twice
20 recrystallized from ethyl acetate/methanol to yield 1-(p-
nitrophenoxy)-2,3,4,5-tetrahydro-3-benzazepine hydro-
chloride, d 227-228°C.

ANALYSIS:

Calculated for C₁₆H₁₆N₂O₃.HCl: 59.91%C 5.34%H 8.74%N
25 Found: 59.77%C 5.30%H 8.37%N

E x a m p l e 4

1-(m-Chlorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine

oxalate

A solution of 1-hydroxy-2,3,4,5-tetrahydro-3-benz-
30 azepine (14.0 g., 0.086 mole) in DMF (90 ml) was added at
room temperature to a suspension of sodium hydride (5.0 g.
50 % (98 %) oil dispersion, 0.10 mole, washed twice with
hexane) in DMF (25 ml). The mixture was stirred at room
temperature for one hour, warmed briefly at 50°C and
35 cooled. A solution of 1-chloro-3-fluorobenzene (12.9 g,
0.10 mole) in DMF (15 ml) was added thereto. The resultant

reaction mixture was stirred at room temperature overnight (about 16 hours) then at 70°C for one hour. The mixture was cooled, then concentrated to an oil which was stirred with water and then extracted with dichloromethane. The organic phases were washed twice with water then dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered then concentrated to an oil which was dissolved in ether and then converted to the oxalate salt as in Example 1 (14.5 g, 46 %, d 196-200°C). 4.5 g of the resultant oxalate salt was twice recrystallized from ethyl acetate/methanol solution to yield 1-(m-chlorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine oxalate, d 202-202.5°C.

ANALYSIS:

Calculated for C₁₆H₁₆ClNO₂(CO₂H)₂: 59.42 %C 4.99%H 3.85%N
Found: 59.20%C 5.15%H 3.84%N

Example 5

1-(m-Chlorophenoxy)-3-(3-N,N-dimethylaminopropyl)-2,3,4,5-tetrahydro-3-benzazepine dioxalate

A mixture of 1-(m-chlorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine of Example 4, (6.4 g., 0.023 mole), 3-dimethylaminopropyl chloride (5.7 g, 0.047 mole), potassium carbonate (10.0 g) and 0.01 g of potassium iodide in n-butanol (100 ml) was refluxed for three hours. The reaction mixture was cooled, then concentrated to an oil which was stirred with water and then extracted with ether and then with chloroform. The combined organic phases were washed twice with water, then dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered, then concentrated to an oil (7.5 g) which was dissolved in ether, then converted to the dioxalate salt (7.0 g., 56 %, d 82-115°C) utilizing the procedure of Example 1. This material was twice recrystallized from a 20:1 ethyl acetate/methanol solution to yield 1-(m-chlorophenoxy)-3-(3-N,N-dimethylamino-propyl)-2,3,4,5-tetrahydro-3-benzazepine dioxalate (3.5 g, d 190-190.5°).

ANALYSIS:

Calculated for $C_{21}H_{27}ClN_2O \cdot 2C_2H_2O_4$: 55.71%C 5.80%H 5.20%N
Found: 55.75%C 5.93%H 5.18%N

E x a m p l e 6

5 1-(m-Trifluoromethylphenoxy)-2,3,4,5-tetrahydro-3-
benzazepine hydrobromide
A solution of 1-hydroxy-2,3,4,5-tetrahydro-3-benz-
azepine (8.0 g., 0.049 mole) in DMF (90 ml) was added at
room temperature to a suspension of sodium hydride (2.9 g
10 50 % oil dispersion (98 %), 0.059 mole, washed twice with
hexane) in DMF (25 ml). The mixture was warmed to 45°C
for one hour, cooled to room temperature, and a solution
of m-fluorobenzotrifluoride (9.3 g., 0.056 mole) in DMF
(20 ml) was added. The mixture was stirred at room
15 temperature overnight. The solvent was removed in vacuo to
yield an oil which was stirred with water, then extracted
with dichloromethane. The organic extracts were washed
twice with water, then dried (saturated NaCl, anhydrous
 $MgSO_4$). The solution was filtered, then concentrated to
20 an oil (9.5 g) which was dissolved in ether, then con-
verted to the hydrobromide salt by the addition of ethereal
HBr (4.0 g., 38 %, d 109-110°C). This material was twice
recrystallized from a 25:1 ethyl acetate/methanol solution
to yield 1-(m-trifluoromethylphenoxy)-2,3,4,5-tetrahydro-
25 3-benzazepine hydrobromide, d 111°C.

ANALYSIS:

Calculated for $C_{17}H_{16}F_3NO \cdot HBr$: 52.59%C 4.41%H 3.61%N
Found: 52.44%C 4.24%H 3.39%N

E x a m p l e 7

30 1-(m-Chlorophenoxy)-3-methyl-2,3,4,5-tetrahydro-3-
benzazepine

To a cooled solution of 1-(m-chlorophenoxy)-2,3,4,5-
tetrahydro-3-benzazepine of Example 4, (6.5 g, 0.024 mole)
and triethylamine (2.8 g, 0.028 mole) in chloroform
35 (75 ml) was slowly dropped ethyl chloroformate (3.0 g,
0.028 mole) in chloroform (10 ml). The reaction mixture
was stirred overnight, about 16 hours, at ambient

temperature, then was concentrated to an oil which was dissolved in ether, washed with water, dilute HCl, again twice washed with water, then dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered, then concentrated to an oil (7.5 g, 90 %). A solution of the oil in tetrahydrofuran (THF) (75 ml) was slowly dropped into a refluxing suspension of LiAlH₄ (1.6 g. 0.042 mole) in THF (125 ml). After refluxing five hours, the mixture was cooled, then was quenched by dropwise addition of saturated NH₄Cl solution. The mixture was diluted with ether, filtered, washed twice with water then dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered, then concentrated to an oil (5.6 g., 93 %). This oil was distilled to yield an oil of 1-(m-chlorophenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine (150-170°C/0.1 mm).

ANALYSIS:

Calculated for C₁₇H₁₈ClNO: 70.95%C 6.30%H 4.87%N

Found: 71.23%C 6.40%H 4.69%N

Example 8

3-(3-N,N-Dimethylaminopropyl)-2,3,4,5-tetrahydro-1-(p-trifluoro-methylphenoxy)-3-benzazepine dihydrochloride

A mixture of 2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 1, (6.2 g, 0.020 mole), 3-dimethylaminopropyl chloride (4.9 g. 0.040 mole), 25 potassium carbonate (10 g) and potassium iodide in n-butanol (100 ml) was refluxed three hours. The mixture was cooled, filtered, then concentrated to an oil which was stirred with water then extracted with ether and then with chloroform. The organic extracts were washed twice with water, then dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered then concentrated to an oil (5.8 g) which was dissolved in ether and then converted to the dihydrochloride salt (hygroscopic) by the addition of ethereal-HCl. This material was immediately recrystallized from a 25:1 solution of ethyl acetate/methanol to yield 30 3-(3-N,N-dimethylaminopropyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine dihydrochloride,

(3.0 g, 32 %, d 235-236°C).

ANALYSIS:

Calculated for $C_{22}H_{27}F_3N_2O.2HCl$: 56.78%C 6.28%H 6.02%N
Found: 56.43%C 6.14%H 5.75%N

5 Example 9

a) 3-Phenylacetyl-2,3,4,5-tetrahydro-1-(p-trifluoromethyl-phenoxy)-3-benzazepine

To a cooled solution of 2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 1 (5.8 g. 0.019 mole) and triethylamine (2.3 g, 0.023 mole) in chloroform (75 ml) was slowly dropped phenylacetyl chloride (3.5 g. 0.023 mole) in chloroform (10 ml). After stirring at ambient temperature overnight the reaction mixture was concentrated to an oil. The oil was dissolved in ether, then washed with water, dilute HCl (10 %), again with water and dried (saturated NaCl, anhydrous $MgSO_4$). The solution was filtered, concentrated to an oil which was extracted with boiling hexanes and then concentrated to an oil (6.8 g, 84 %). A sample was distilled to yield an oil of 3-phenylacetyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine, 240-250°C /0.1 mm.

ANALYSIS:

Calculated for $C_{25}H_{22}F_3NO_2$: 70.57%C 5.21%H 3.29%N
25 Found: 70.28%C 5.19%H 2.98%N

b) 3-(2-Phenylethyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethyl-phenoxy)-3-benzazepine

A solution of 3-phenylacetyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 9a (6.5 g, 0.015 mole) in THF (100 ml) was slowly dropped into a refluxing suspension of $LiAlH_4$ (1.2 g, 0.030 mole) in THF (75 ml). After refluxing four hours the mixture was cooled, then quenched by dropwise addition of saturated NH_4Cl . The mixture was diluted with ether, filtered, washed twice with water and dried (saturated NaCl, anhydrous $MgSO_4$). The solution was filtered, then concentrated to an oil (6.2 g., 92%). This oil was

distilled to yield an oil of 3-(2-phenylethyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine, 220-235°C / 0.1 mm.

ANALYSIS:

5 Calculated for $C_{25}H_{24}F_3NO$: 72.97% C 5.88% H 3.41% N
Found: 72.72% C 5.65% H 3.33% N

Example 10

1-(m-Chlorophenoxy)-3-(2-phenylethyl)-2,3,4,5-tetrahydro-3-benzazepine oxalate

10 A solution of phenylacetyl chloride (4.3 g, 0.028 mole) in chloroform (10 ml) was slowly dropped into a cooled solution of 1-(m-chlorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine of Example 4 (6.5 g, 0.024 mole) and triethylamine (2.8 g, 0.028 mole) in chloroform (75 ml).

15 After stirring at ambient temperature overnight, the reaction mixture was concentrated to an oil which was dissolved in ether, then washed with water, dilute HCl (10 %), twice with water and dried (saturated NaCl, anhydrous $MgSO_4$). The solution was filtered, then concentrated to an oil (9.5 g). This oil was dissolved in tetrahydrofuran (THF) (75 ml) and slowly dropped into a refluxing suspension of $LiAlH_4$ (1.6 g, 0.042 mole) in THF (125 ml). After refluxing five hours, the reaction mixture 20 was cooled, then quenched by drop-wise addition of saturated NH_4Cl (50 ml). The mixture was diluted with ether, filtered, washed twice with water and dried (saturated NaCl, anhydrous $MgSO_4$). The solution was filtered, then concentrated to an oil (8.0 g, 88 %). This 25 oil was dissolved in ether then converted to the oxalate salt to yield 1-(m-chlorophenoxy)-3-(2-phenylethyl)-2,3,4,5-tetrahydro-3-benzazepine oxalate (2.4 g, d.p. 95-96°C), using the procedure of Example 1.

ANALYSIS:

30 Calculated for $C_{24}H_{24}ClNO.(CO_2H)_2$: 66.73% C 5.60% H 2.99% N
Found: 66.60% C 5.32% H 2.75% N

Example 11

a) 3-Ethoxycarbonyl-2,3,4,5-tetrahydro-1-(p-trifluoromethyl-phenoxy)-3-benzazepine

To a cooled solution of 2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 1 (6.3 g, 0.021 mole) and triethylamine (2.1 g, 0.024 mole) in chloroform (70 ml) was slowly dropped a solution of ethyl chloroformate (2.6 g, 0.024 mole) in chloroform (20 ml). After stirring six hours at ambient temperature the reaction mixture was concentrated to an oil. The oil was dissolved in ether, washed with water, dilute HCl, again twice with water and then dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered and then concentrated to yield an oil (8.0 g). A sample was distilled to yield an oil of 3-ethoxycarbonyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine, 195°C /0.1 mm.

ANALYSIS:

Calculated for C₂₀H₂₀F₃NO₃: 63.32%C 5.31%H 3.69%N
20 Found: 63.44%C 5.35%H 3.55%N

b) 3-Methyl-2,3,4,5-tetrahydro-1-(p-trifluoromethyl-phenoxy)-3-benzazepine hydrochloride

A solution of 3-ethoxycarbonyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 11a (7.0 g. 0.018 mole) in THF (100 ml) was slowly dropped into a refluxing suspension of LiAlH₄ (1.4 g. 0.036 mole) in THF (75 ml). After refluxing four hours, the reaction mixture was cooled, then quenched by dropwise addition of saturated NH₄Cl. The mixture was diluted with ether, filtered, washed twice with water and dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered, then concentrated to an oil (5.1 g), which was dissolved in ether and converted to the hydrochloride salt (5.1 g., 80 %, d 203-206°C) by the addition of ethereal HCl. This material was twice recrystallized from ethyl acetate/methanol solution to yield 3-methyl-2,3,4,5-tetrahydro-

1-(p-trifluoromethylphenoxy)-3-benzazepine hydrochloride,
d 210-211°C.

ANALYSIS:

Calculated for $C_{18}H_{18}F_3NO \cdot HCl$: 60.42% C 5.35% H 3.92% N

5 Found: 60.84% C 5.20% H 3.66% N

Example 12

1-(m-Chlorophenoxy)-3-(n-propyl)-2,3,4,5-tetrahydro-3-benzazepine

A mixture of 1-(m-chlorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine of Example 4 (6.4 g, 0.023 mole), 1-bromo-propane (5.7 g., 0.047 mole) and sodium bicarbonate (8.4 g, 0.10 mole) in DMF (100 ml) was stirred at 70°C for three hours. The mixture was concentrated under high vacuum to an oil which was stirred with water then extracted with ether. The ether extracts were washed twice with water and dried (saturated NaCl, anhydrous $MgSO_4$). The solution was filtered, then concentrated to an oil (6.3 g, 86 %) which was distilled to yield an oil of 1-(m-chlorophenoxy)-3-(n-propyl)-2,3,4,5-tetrahydro-3-benzazepine,
20 190-210°C/0.1 mm.

ANALYSIS:

Calculated for $C_{19}H_{22}ClNO$: 72.25% C 7.02% H 4.44% N

Found: 71.93% C 7.02% H 4.20% N

Example 13

1-(m-Chlorophenoxy)-3-cyclopropylmethyl-2,3,4,5-tetrahydro-3-benzazepine oxalate

A mixture of 1-(m-chlorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine of Example 4, (7.0 g. 0.026 mole), chloromethylcyclopropane (4.6 g, 0.051 mole) and sodium bicarbonate (8.4 g, 0.10 mole) in DMF (85 ml) was warmed at 80-90°C for four hours. The reaction mixture was cooled, then concentrated under high vacuum to an oil which was stirred with water and extracted with ether. The ether extracts were twice washed with water and dried (saturated NaCl, anhydrous $MgSO_4$). The solution was filtered, then concentrated to an oil which was dissolved in ether and then converted to the oxalate salt (7 g, mp

at 80-95°C) using the procedure of Example 1. This material was rebasified, then passed through a silica gel dry column with ethyl acetate as eluent. The desired product was extracted with ethyl acetate, then concentrated to an oil (3.8 g). This oil was converted to the oxalate salt using the procedure of Example 1 and then immediately recrystallized from a 20:1 solution of ethyl acetate/methanol to yield 1-(m-chlorophenoxy)-3-cyclopropylmethyl-2,3,4,5-tetrahydro-3-benzazepine oxalate, (3.1 g, d 100-101°C).

ANALYSIS:

Calculated for $C_{20}H_{22}ClNO \cdot (CO_2H)_2$: 63.23% C 5.79% H 3.35% N
Found: 63.04% C 5.78% H 3.35% N

Example 14

15. 3-[2-(p-Nitrophenylethyl)]-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine hydrobromide
A mixture of 2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 1 (13.0 g, 0.042 mole), p-nitrophenethyl bromide (11.7 g, 0.05 mole), sodium bicarbonate (18 g, 0.21 mole) and 0.01 g of KI in DMF (100 ml) was warmed at 90°C for six hours. The reaction mixture was cooled, filtered and concentrated to an oil which was stirred with water then extracted with ether. The ether extracts were washed with water and dried (saturated $MgSO_4$). The solution was filtered then concentrated to an oil (20 g). The oil was passed through a silica gel dry column using ethyl acetate as the eluent. The desired product was extracted with ethyl acetate, filtered and concentrated to an oil (16 g) which was dissolved in ether, then converted to the hydrobromide salt (8 g, 35%, m.p. 98-108°C) by the addition of ethereal HBr. A 3.0 g sample was recrystallized from a 20:1 solution of ethyl acetate/methanol to yield 3-[2-(p-nitrophenylethyl)]-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine hydrobromide (2.4 g, d 216-217°C). ^{1H} NMR (CDCl₃) δ 1.0-4.0 ppm.

ANALYSIS:

Calculated for $C_{25}H_{23}F_3N_2O_3 \cdot HBr$: 55.87% C 4.50% H 5.21% N
Found: 55.69% C 4.61% H 5.20% N

E x a m p l e 15

5

3-[2-(4-Aminophenylethyl)]-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine dioxalate

10

A solution of 3-[2-(p-nitrophenylethyl)]-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine hydrobromide of Example 14 (6.0 g., 0.011 mole) in glacial acetic acid (50 ml) was dropped into a stirred suspension of zinc dust (3.5 g., 0.049 mole) in 50 % aqueous acetic acid (60 ml). After stirring one hour at ambient temperature, the mixture was filtered and the zinc and inorganic salts were washed with 3N HCl. The filtrate was basified with 6N NaOH and extracted with ether. The ether extracts were washed twice with water and dried (saturated NaCl, anhydrous $MgSO_4$). The solution was filtered and concentrated to an oil (4.5 g) which was dissolved in ether and converted to the dioxalate salt (5.5 g, 82 %, $d 120-140^\circ C$) using the procedure of Example 1. This material was recrystallized from a solution of ethyl acetate/methanol to yield 3-[2-(4-aminophenylethyl)]-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine dioxalate, $d 157-158^\circ C$.

15

ANALYSIS:

Calculated for $C_{25}H_{25}F_3N_2O_2(CO_2H)_2$: 57.42% C 4.82% H 4.62% N
Found: 57.16% C 4.71% H 4.62% N

E x a m p l e 16

30

a) 3-Propionyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine

35

To a cooled solution of 2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 1 (6.5 g, 0.021 mole) and triethylamine (2.5 g, 0.025 mole) in chloroform (75 ml) was slowly dropped propionyl chloride (2.3 g, 0.025 mole) in chloroform (10 ml). After stirring at ambient temperature two hours the reaction mixture was

concentrated to an oil which was dissolved in ether then washed with water, dilute HCl, again twice with water and dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered, then concentrated to a solid (7.2 g, 95 %, m.p.

5 98-105°C). A sample was twice recrystallized from hexanes to yield 3-propionyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine, m.p. 109-110°C.

ANALYSIS:

Calculated for C₂₀H₂₀F₃NO₂: 66.10%C 5.55%H 3.86%N

10 Found: 65.99%C 5.52%H 3.75%N

b) 3-(n-Propyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine hydrobromide

A solution of 3-propionyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 16a (6.5 g, 0.018 mole) in THF (100 ml) was dropped into a refluxing suspension of LiAlH₄ (1.4 g, 0.036 mole) in THF (75 ml). After refluxing four hours, the reaction mixture was cooled, diluted with ether and quenched by dropwise addition of saturated NH₄Cl. The mixture was filtered,

15 washed twice with water and was dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered and concentrated to an oil (5.0 g) which was passed through a silica gel dry column using ethyl acetate as the eluent. The desired product was extracted with ethyl acetate,

20 filtered and concentrated to an oil (5.2 g). The oil was then distilled to yield an oil (3.9 g, 62 %, 180-185°C / 0.1 mm). This oil was dissolved in ether, filtered, and converted to the hydrobromide salt by the addition of ethereal HBr which was recrystallized from a 20:1 solution 25 of ethyl acetate/methanol to yield 3-(n-propyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine hydrobromide (3.5 g, 45 %, d 193°C).

ANALYSIS:

Calculated for C₂₀H₂₂F₃NO.HBr: 55.82%C 5.39%H 3.26%N

30 Found: 55.42%C 5.24%H 3.18%N

new entries not to be used

Example 17

3-Cyclopropylmethyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine hydrobromide

A mixture of 2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 1, (7.0 g, 0.023 mole), chloromethylcyclopropane (4.1 g, 0.046 mole), sodium bicarbonate (8.4 g, 0.10 mole) and 0.01 g of KI in DMF (85 ml) was warmed at 75-80°C for five hours. The reaction mixture was cooled, then concentrated under high vacuum to an oil which was stirred with water and extracted with ether. The ether extracts were washed twice with water and dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered and concentrated to an oil (7 g) which was passed through a silica gel dry column with ethyl acetate as the eluent. The desired product was extracted with ethyl acetate, filtered and concentrated to an oil (6 g) which was distilled to yield an oil (3.5 g). This oil was converted to the hydrobromide salt by the addition of ethereal HBr and immediately recrystallized from a 25:1 solution of ethyl acetate/methanol to yield 3-cyclopropylmethyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine hydrobromide (1.4 g, 14 %, d 198-198.5°C).

ANALYSIS:

Calculated for C₂₁H₂₂F₃NO.HBr: 57.02%C 5.24%H 3.17%N
Found: 56.78%C 5.16%H 3.10%N

Example 18

a) 3-Cyanomethyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine

A mixture of 2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 1 (16 g, 0.052 mole), chloroacetonitrile (8 g, 0.010 mole) and sodium bicarbonate (17 g, 0.20 mole) in DMF (125 ml) was warmed at 70°C for 2.5 hours. The mixture was concentrated to an oil which was stirred with water and extracted with ethyl acetate. The organic extracts were washed twice with water and

dried (saturated NaCl, anhydrous MgSO₄). After filtering, the solvent was evaporated to an oil (18 g) which solidified upon triturating with petroleum ether to a solid (16.5 g, 92 %, m.p. 125-129°C). A sample was recrystallized from 5 hexanes to yield 3-cyanomethyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine, m.p. 134-135°C.

ANALYSIS:

Calculated for C₁₉H₁₇F₃N₂O: 65.88%C 4.95%H 8.09%N 16.46%F

Found: 65.56%C 4.91%H 7.96%N 16.03%F

10 b) 3-(2-Aminoethyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine dioxalate

A solution of 3-cyanomethyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 18a. (16 g, 0.046 mole) in THF (100 ml) was dropped into a. 15 suspension of LiAlH₄ (7.2 g, 0.19 mole) in THF (100 ml). After refluxing for twenty hours the mixture was cooled, then quenched by dropwise addition of saturated NH₄Cl. The mixture was diluted with ether, filtered, washed twice with water and dried (saturated NaCl, anhydrous MgSO₄). 20 The solution was filtered and evaporated to an oil (14 g) of which 3 g was converted to the dioxalate salt (4.5 g, d 160-165°C) using the procedure of Example 1. This material was twice recrystallized from a 20:1 solution of ethyl acetate/methanol to yield 3-(2-aminoethyl-2,3,4,5- 25 tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine dioxalate (2.3 g, d 173-174°C).

ANALYSIS:

Calculated for C₁₉H₂₁F₃N₂O₂(CO₂H)₂: 52.07%C 4.75%H 5.28%N

Found: 51.67%C 4.75%H 5.31%N

30 Example 19

7,8-Dimethoxy-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine oxalate

A solution of 7,8-dimethoxy-1-hydroxy-2,3,4,5-tetrahydro-3-benzazepine (9 g, 0.040 mole) in DMF (50 ml) 35 was added at room temperature to a suspension of sodium hydride (2.4 g, 50 % oil dispersion, 0.048 mole) (washed

twice with hexane) in DMF (10 ml). The mixture was stirred at 70°C for one hour, then was cooled to 50°C and a solution of p-fluorobenzotrifluoride (8 g, 0.048 mole) in DMF (10 ml) was added. After stirring twenty hours at ambient temperature, the mixture was concentrated to an oil which was stirred with water and extracted with ethyl acetate-ether. The combined organic phases were washed twice with water and dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered, then concentrated to an oil which was dissolved in ether then converted to the oxalate salt (10 g, 55 %, d 110°C), using the procedure of Example 1. 3.0 g of material was twice recrystallized from a 20:1 ethyl acetate/methanol solution to yield 7,8-dimethoxy-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine oxalate, d 143-144°C.

ANALYSIS:

Calculated for C₁₉H₂₀F₃NO₃·(CO₂H)₂: 55.14%C 4.85%H
Found: 55.00%C 5.17%H.

Example 20

20 a) 7,8-Dimethoxy-3-ethoxycarbonyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine
To a cooled solution of 7,8-dimethoxy-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine (5.5 g, 0.015 mole) and triethylamine (1.7 g, 0.017 mole) in chloroform (70 ml) was slowly dropped a solution of ethyl chloroformate (1.0 g, 0.017 mole) in chloroform (20ml). After stirring twenty hours at ambient temperatures the reaction mixture was concentrated to an oil which was dissolved in ether, washed with water, dilute HCl, again twice with water, then dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered then concentrated to a solid (5.0 g, 76%, m.p. 120°C) of which a sample was twice recrystallized from hexanes to yield 7,8-dimethoxy-3-ethoxycarbonyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine, m.p. 130-131°C.

ANALYSIS:

Calculated for $C_{22}H_{24}F_3NO_5$: 60.13% C 5.51% H

Found: 60.34% C 5.42% H

5 b) 7,8-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine hydrochloride

A solution of 7,8-dimethoxy-3-ethoxycarbonyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 20a, (4.5 g, 0.010 mole) in THF (60 ml) was slowly dropped into a stirred suspension of $LiAlH_4$ (0.8 g, 0.020 mole) in THF (100 ml). After refluxing three hours, the reaction mixture was cooled, diluted with ether, then quenched by dropwise addition of saturated NH_4Cl (60 ml). The mixture was filtered and the organic layer was washed twice with water and dried (saturated 15 $NaCl$, anhydrous $MgSO_4$). The solution was filtered, then concentrated to an oil which was dissolved in ether and converted to the hydrochloride salt (4.0 g, 95% d 188-190°C) by the addition of ethereal HCl. This material was twice recrystallized from a 20:1 solution of ethyl acetate/methanol to yield 7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine hydrochloride, d 204-205°C.

20

25 ANALYSIS:

Calculated for $C_{20}H_{22}F_3NO_3 \cdot HCl$: 57.49% C 5.55% H 3.35% N

Found: 57.55% C 5.64% H 3.29% N

Example 21

a) 3-Cyanomethyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine

A mixture of 7,8-dimethoxy-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine (11 g, 0.030 mole), chloroacetonitrile (4.5 g, 0.060 mole) and sodium bicarbonate (10 g, 0.12 mole) in DMF (125 ml) was stirred at 75-80°C for two hours. The mixture was concentrated to an oil which was stirred with water and extracted with 30 ethyl acetate-ether. The organic layers were washed twice with water and dried (saturated $NaCl$, anhydrous $MgSO_4$).

35

The solution was filtered and concentrated to an oil (12 g, 95 %) which was extracted with boiling hexanes to yield a solid (7 g, m.p. 83-88°C). A sample was recrystallized from hexanes to yield 3-cyanomethyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine, m.p. 93-94°C.

ANALYSIS:

Calculated for $C_{21}H_{21}F_3N_2O_3$: 62.06 %C 5.21%H

Found: 61.79%C 5.14%H

10 b) 3-(2-Aminoethyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine dioxalate

A solution of 3-cyanomethyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 21a (12 g, 0.030 mole) in THF (100 ml) was dropped 15 into a stirred suspension of $LiAlH_4$ (4.6 g, 0.12 mole) in THF (200 ml). After stirring at reflux for four hours, the mixture was cooled, diluted with ether, then quenched by dropwise addition of saturated NH_4Cl (20 ml). The mixture was filtered, washed twice with water and dried 20 (saturated $NaCl$, anhydrous $MgSO_4$). The solution was filtered, then concentrated to an oil (9.2 g, 75 %) which was dissolved in ether and converted to the dioxalate salt (11 g, d 130-135°C) using the procedure of Example 1. 4.0 g, of material was twice recrystallized from methanol/ether to yield 3-(2-aminoethyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine dioxalate, d 139-140°C.

ANALYSIS

Calculated for $C_{21}H_{25}F_3N_2O_3 \cdot 2(CO_2H)_2$: 50.85%C 4.95%H

30 Found: 50.70%C 4.94%H

Example 22

1-(m-Chlorophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine oxalate

A solution of 7,8-dimethoxy-1-hydroxy-2,3,4,5-tetrahydro-3-benzazepine (6.5 g, 0.029 mole) in DMF (50 ml)

was added at room temperature to a suspension of sodium hydride (1.7 g, 50 % oil dispersion, 0.034 mole, washed twice with hexane) in DMF (10 ml). The mixture was warmed to 70°C for one hour, then was cooled to 50°C, and a 5 solution of 1-chloro-3-fluorobenzene (4.6 g, 0.034 mole) in DMF (10 ml) was slowly added. After stirring four hours, the mixture was cooled, then concentrated to an oil which was stirred with water and extracted with ethyl acetate. The organic extracts were washed twice with water, then 10 dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered then concentrated to an oil (8 g, 82%), which was purified by column chromatography (silica gel, eluted with 20 % C₂H₅OH/CHCl₃) to yield an oil (2.0 g) which was converted to the oxalate salt, using the procedure of 15 Example 1 (2.3 g, d 130-140°C), then recrystallized from a 25:1 solution of ethyl acetate/methanol to yield 1-(m-chlorophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine oxalate (2.0 g, d 177-178°C).

ANALYSIS:

20 Calculated for C₁₈H₂₀ClNO₃·(CO₂H)₂: 56.67%C 5.23%H
Found: 56.52%C 5.16%H

Example 23

a) 3-(2-Ethoxycarbonylaminoethyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine
25 To a cooled solution of 3-(2-aminoethyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 19b (5.5 g, 0.016 mole) and triethylamine (1.8 g, 0.018 mole) in chloroform (75 ml) was slowly dropped a solution of ethyl chloroformate (2.0 g, 0.18 mole) in 30 chloroform (25 ml). After stirring twenty hours at ambient temperature the reaction mixture was concentrated to a semisolid which was dissolved in ether, washed with water and dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered and concentrated to yield an oil. A sample of 35 the resultant oil was distilled to yield an oil of 3-(2-ethoxycarbonylaminoethyl)-2,3,4,5-tetrahydro-1-(p-

trifluoromethylphenoxy)-3-benzazepine, bp 235-238°C/
0.10 mm.

ANALYSIS:

Calculated for $C_{22}H_{25}F_3N_2O_3$: 62.55% C 5.97% H

5 Found: 62.69% C 5.88% H

b) 3-(2-Methylaminoethyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine dioxalate

10 A solution of 3-(2-ethoxycarbonylaminoethyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of

Example 23a (5.0 g, 0.012 mole) in THF (75 ml) was slowly dropped into a stirred suspension of $LiAlH_4$ (0.9 g, 0.024 mole) in THF (25 ml). After refluxing two hours, the reaction mixture was cooled, diluted with ether, then quenched by dropwise addition of saturated NH_4Cl (25 ml).

15 The mixture was filtered, and the organic filtrate was washed twice with water and dried (saturated NaCl, anhydrous $MgSO_4$). The solution was filtered, then concentrated to an oil (4.9 g) which was converted using the procedure of Example 1 to the dioxalate salt (6 g, 92 %, d 199-201°C). This material was twice recrystallized from methanol to yield 3-(2-methylaminoethyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine dioxalate, d 207-208°C.

20 ANALYSIS:
25 Calculated for $C_{20}H_{23}F_3N_2O_2 \cdot 2(CO_2H)_2$: 52.94% C 5.00% H
Found: 53.05% C 5.13% H

Example 24

a) 3-Cyanomethyl-2,3,4,5-tetrahydro-1-(m-trifluoromethylphenoxy)-3-benzazepine

30 A mixture of 2,3,4,5-tetrahydro-1-(m-trifluoromethylphenoxy)-3-benzazepine of Example 6 (10 g, 0.033 mole), chloroacetonitrile (4.9 g, 0.065 mole) and sodium bicarbonate (11 g, 0.13 mole) in DMF (100 ml) was stirred at 55-60°C for three hours. The mixture was concentrated
35 to an oil which was stirred with water and extracted with ether. The organic extracts were washed twice with water and dried (saturated NaCl, anhydrous, $MgSO_4$). The solution

was filtered and concentrated to an oil (11 g, 96 %) of which 3.8 g was distilled to yield 2.4 g. of an oil of 3-cyanomethyl-2,3,4,5-tetrahydro-1-(m-trifluoromethylphenoxy)-3-benzazepine (220-223°C /0.10 mm).

5 ANALYSIS:

Calculated for $C_{19}H_{17}F_3N_2O$: 65.88% C 4.95% H

Found: 65.97% C 4.99% H

b) 3-(2-Aminoethyl)-2,3,4,5-tetrahydro-1-(m-trifluoromethylphenoxy)-3-benzazepine dioxalate

10 A solution of 3-cyanomethyl-2,3,4,5-tetrahydro-1-(m-trifluoromethylphenoxy)-3-benzazepine of Example 24a (8 g, 0.023 mole) in THF (100 ml) was dropped into a stirred suspension of $LiAlH_4$ (3.5 g, 0.092 mole) in THF (100 ml) and stirred at ambient temperature for one hour. The mixture was then cooled, diluted with anhydrous ether, quenched by slow addition of saturated NH_4Cl , then was filtered, washed twice with water and was dried (saturated $NaCl$, anhydrous $MgSO_4$). The solution was then filtered and concentrated to an oil (6.8 g) which was converted using the procedure of Example 1 to the dioxalate salt (7.5 g, 50%, d 160-163°C). This material was twice recrystallized from a 25:1 ethyl acetate-methanol solution to a solid of 3-(2-aminoethyl)-2,3,4,5-tetrahydro-1-(m-trifluoromethylphenoxy)-3-benzazepine dioxalate, d 170-171°C.

15

20

25

ANALYSIS:

Calculated for $C_{19}H_{21}F_3N_2O.2(CO_2H)_2$: 52.07% C 4.75% H

Found: 52.15% C 4.86% H

Example 25

30 3-(2-Aminoethyl)-1-(m-chlorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine dioxalate

A mixture of 1-(m-chlorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine of Example 4 (8.0 g, 0.029 mole), chloroacetonitrile (4.4 g, 0.058 mole) and sodium bicarbonate (10 g, 0.12 mole in DMF (100 ml) was stirred at 65°C for 2.5 hours. The mixture was concentrated to an oil which was stirred with water and extracted with ether. The organic

35

extracts were washed twice with water and dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered and concentrated to an oil (8 g) which was extracted with boiling hexanes and concentrated to a light solid (5.4 g, 5 62 %, m.p. 89.95°C). A solution of 1-(m-chlorophenoxy)-3-cyanomethyl-2,3,4,5-tetrahydro-3-benzazepine (5.1 g, 0.017 mole) in THF (50 ml) was dropped into a stirred suspension of LiAlH₄ (2.6 g, 0.068 mole) in THF (100 ml). After stirring three hours at ambient temperature, the 10 reaction mixture was cooled, diluted with ether, then quenched by dropwise addition of saturated NH₄Cl. The mixture was filtered, and the organic filtrate was washed twice with water and dried (saturated NaCl, anhydrous MgSO₄). The solution was filtered and concentrated to 15 an oil (3.7 g) which was converted using the procedure of Example 1 to the dioxalate salt (5.5 g, 65 %, d 150-155°C). This material was twice recrystallized from a 20:1 solution of ethyl acetate/methanol to yield 3-(2-aminoethyl)-1-(m-chlorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine 20 dioxalate, d 172-173°C.

ANALYSIS:

Calculated for C₁₈H₂₁ClN₂0.2(CO₂H)₂: 53.17%C 5.07%H

Found: 53.47%C 5.12%H

Example 26

25 3-(2-Dimethylaminoethyl)-1-p-trifluoromethylphenoxy)-3-benzazepine dihydrochloride

A mixture of 2,3,4,5-tetrahydro-1-(p-trifluoro-methylphenoxy)-3-benzazepine of Example 1 (8.5 g, 0.028 mole), 2-dimethylaminoethyl chloride hydrochloride (6.5 g, 30 0.045 mole) and sodium bicarbonate (18 g, 0.21 mole) in DMF (125 ml) was stirred at 60°C for two hours. The reaction mixture was concentrated to a slurry which was stirred with water and extracted with ethyl acetate-ether. The organic extracts were washed twice with water and dried (saturated NaCl, anhydrous MgSO₄). The solution 35 was filtered and concentrated to an oil (8 g) which was converted to the dihydrochloride salt (6 g, 48 % d 170°C)

by the addition of ethereal HCl. This material was recrystallized twice from a 20:1 ethyl acetate/methanol solution to yield 3-(2-dimethylaminoethyl)-1-(p-trifluoromethylphenoxy)-3-benzazepine dihydrochloride,

5 d 237-238°C.

ANALYSIS:

Calculated for $C_{21}H_{25}F_3N_2O \cdot 2HCl$: 55.88%C 6.03%H

Found: 55.87%C 5.94%H

Example 27

10 a) 3-(2-Cyanoethyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine

A solution of 2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 1 (15 g, 0.049 mole) and acrylonitrile (5.2 g, 0.098 mole) in isopropanol (50 ml) was stirred at reflux (95°C) for twenty hours. The reaction mixture was cooled then concentrated to an oil (17 g, 96%) of which 3.5 g was distilled to an oil of 3-(2-cyanoethyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine (2.6 g, 235-237°C/0.1 mm).

15 ANALYSIS:

Calculated for $C_{20}H_{19}F_3N_2O$: 66.65%C 5.31%H 7.78%N

Found: 66.75%C 5.31%H 7.78%N

b) 3-(3-Aminopropyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine dimaleate

20 A solution of 3-(2-cyanoethyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine of Example 27a in THF (10 ml) was slowly dropped into a stirred solution of borane in THF (20 mmole, 20 ml), cooled with an ice bath. After the addition was completed, the reaction mixture was stirred at ambient temperature overnight (about 16 hours). The mixture was cooled and quenched by slow addition of HCl (3N, 25 ml) and then refluxed for thirty minutes. The reaction mixture was again cooled, diluted with water, basified with saturated sodium carbonate and extracted with ether. The organic extract was washed twice with water and dried (saturated NaCl, anhydrous

$MgSO_4$). The solution was filtered and concentrated to an oil (3 g) which was dissolved in ether, then converted to the dimaleate salt by the addition of an ethereal-maleic acid solution (5 g, 95 %, m.p. 145-149°C). This material 5 was recrystallized from ethyl acetate(methanol) to yield 2.8 g of 3-(3-aminopropyl)-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine dimaleate, d 164-165°C.

ANALYSIS:

10 Calculated for $C_{20}H_{23}F_3N_2O.2(C_4H_4O_4)$: 56.37%C 5.24%H
Found: 56.35%C 5.15%H

E x a m p l e 28

a) 1-Phenoxy-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine

15 To a solution of 1-hydroxy-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (10 g, 32 mmole), phenol (3.4 g, 36 mmole) and triphenylphosphine (9.5 g, 36 mmole) in benzene (300 ml), cooled with an ice bath, was slowly dropped a solution of diethyl azodicarboxylate (6.3 g, 20 36 mmole) in benzene (100 ml). After stirring twenty hours at ambient temperature, the reaction mixture was filtered to remove sym-dicarbethoxy-hydrazine. The filtrate was concentrated to an oil which was dissolved in ether and cooled to precipitate the product and triphenylphosphine 25 oxide. The desired product was crystallized from methanol to give a solid of 1-phenoxy-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (6.8 g, 33 %, m.p. 155-156°C).

ANALYSIS:

30 Calculated for $C_{23}H_{23}NO_3S$: 70.20%C 5.89%H
Found: 69.94%C 5.93%H

b) 1-Phenoxy-2,3,4,5-tetrahydro-3-benzazepine hydrochloride

35 A solution of 1-phenoxy-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine of Example 28a (3.0 g, 7.6 mmole) in toluene (10 ml) was added to a solution of sodium bis (2-methoxyethoxy) aluminum hydride

(9.2 g, 45.6 mmole, 70% in toluene) and stirred four days at ambient temperature. The reaction mixture was warmed at 60°C for three hours then was stirred at ambient temperature for twenty hours. The reaction mixture 5 was then cooled, quenched by slow addition of 10% NaOH and separated. The organic layer was washed with water, dried, filtered and concentrated to an oil (1.9 g). The resultant oil was converted to the hydrochloride salt by the addition of ethereal HCl. This material was 10 immediately recrystallized from a 20:1 solution of ethyl acetate/methanol to yield a solid of 1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine hydrochloride (1.4 g, 67%, m.p. 218-220°C).

ANALYSIS:

15 Calculated for $C_{16}H_{17}NO \cdot HCl$: 69.68% C 6.58% H
Found: 69.43% C 6.63% H

Example 29

a) 1-(p-Methylphenoxy)-2,3,4,5-tetrahydro-3-(p-toluene-sulfonyl)-3-benzazepine

20 To a solution of 1-hydroxy-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (18 g, 57 mmole), p-cresol (7 g, 68 mmole) and triphenylphosphine (18 g, 68 mmole) in 300 ml benzene, cooled with an ice bath, was slowly dropped a solution of diethyl azodicarboxylate 25 (12 g, 68 mmole) in 100 ml benzene. After stirring twenty hours at ambient temperature, the reaction mixture was filtered to remove sym-dicarbethoxyhydrazine (10 g, 83%, m.p. 132-135°C) then evaporated to an oil which was purified by column chromatography (silica gel, dichloromethane) to give 16 g of an oil. This oil was purified by high 30 pressure liquid chromatography HPLC (silica gel, 30% hexane in toluene) to give 10 g of product. This material was crystallized from hexane-ether to give 8 g (35%) of 35 1-(p-methylphenoxy)-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine, m.p. 84-86°C.

Calculated for $C_{24}H_{25}NO_3S$: 70.73% C 6.18% H
Found: 70.57% C 6.30% H

b) 1-(p-Methylphenoxy)-2,3,4,5-tetrahydro-3-benzazepine oxalate

A solution of 1-(p-methylphenoxy)-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (3 g, 7.4 mmole) in toluene (15 ml) was added to a solution of sodium bis (2-methoxyethoxy) aluminum hydride (8.9 g, 44.2 mmole, 70 % in toluene), and stirred four days at ambient temperature. The reaction mixture was diluted with ether, quenched by slow addition of 10 % NaOH (10 ml) and was separated. The organic layer was washed with water, dried (saturated NaCl, anhydrous $MgSO_4$), filtered and concentrated to an oil (2.2 g) which was converted utilizing the procedure of Example 1 to the oxalate salt (1.4 g, 55 %, d 219°C). This material was recrystallized from a 20:1 solution of ethyl acetate/methanol to yield 1-(p-methylphenoxy)-2,3,4,5-tetrahydro-3-benzazepine oxalate, m.p. 222-223°C.

ANALYSIS:
Calculated for $C_{17}H_{19}NO \cdot (CO_2H)_2$: 66.46% C 6.16% H
20 Found: 66.20% C, 6.15% H

Example 30

a) 1-(p-Methoxyphenoxy)-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine

To a solution of 1-hydroxy-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (15 g, 47 mmole), p-methoxyphenol (7 g, 57 mmole) and triphenylphosphine (15 g, 57 mmole) in 300 ml benzene, cooled with an ice bath, was slowly dropped a solution of diethyl azodicarboxylate (10 g, 57 mmole) in 100 ml benzene. After stirring two hours at ambient temperature, the reaction mixture was filtered to remove sym-dicarbethoxyhydrazine (8 g, 96 %, m.p. 130-132°C), then evaporated to an oil which was purified by column chromatography (silica gel, dichloromethane) to give an oil. This oil was crystallized from hexane-ether to give 6 g (30 %) of 1-(p-methoxyphenoxy)-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine, m.p. 84-85°C.

Calculated for $C_{24}H_{25}NO_4S$: 68.06%C 5.95%H

Found: 68.13%C 5.85%H

b) 1-(p-Methoxyphenoxy)-2,3,4,5-tetrahydro-3-benzazepine oxalate

5 A solution of 1-(p-methoxyphenoxy)-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (5.0 g, 11.8 mmole) in toluene (30 ml) was added to a solution of sodium bis (2-methoxyethoxy) aluminum hydride (14.3 g, 70.8 mmole, 70 % in toluene) and stirred at ambient
10 temperature twenty hours. The reaction mixture was diluted with ether, quenched by slow addition of 10 % NaOH and separated. The organic layer was washed with water, dried, filtered and concentrated to an oil which was converted using the procedure of Example 1 to the oxalate salt
15 (1.2 g, 28 %, d 186-188°C). This material was recrystallized from a 20:1 solution of ethyl acetate/methanol to give a solid of 1-(p-methoxyphenoxy)-2,3,4,5-tetrahydro-3-benzazepine oxalate, d 201-202°C.

ANALYSIS:

20 Calculated for $C_{17}H_{19}NO_2 \cdot (CO_2H)_2$: 63.50%C 5.89%H

Found: 63.22%C 5.88%H

Example 31

3-Methyl-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine hydrochloride

25 To a cooled solution of 1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine (3.9 g, 16 mmole) of Example 28 b and triethylamine (1.8 g, 18 mmole) in chloroform (50 ml) was slowly added ethyl chloroformate (1.9 g, 18 mmole) in chloroform (10 ml). The reaction mixture was stirred
30 two hours at ambient temperature, then was evaporated to an oil which was stirred with water and extracted with ether. The organic extracts were washed with dilute HCl, water, then dried (saturated NaCl, anhydrous $MgSO_4$). The solution was filtered and concentrated to an oil (4.7 g, 93 %). A solution of the oil in THF (40 ml) was slowly added to a cooled suspension of $LiAlH_4$ (1.7 g, 45 mmole) in THF (100 ml). After stirring three hours at ambient

temperature, the mixture was cooled, diluted with ether, then quenched by slow addition of saturated NH_4Cl . The mixture was filtered, washed with water and dried (saturated NaCl , anhydrous MgSO_4). The solution was 5 filtered and concentrated to an oil which was converted by the addition of ethereal HCl to the hydrochloride salt (3 g 69 %, d 211-214°C). This material was recrystallized from a 20:1 solution of ethyl acetate/methanol to 10 yield 3-methyl-1-phenoxy-2,3,4,5-tetrahydro-3-benz-azepine hydrochloride, d 224-225°C.

ANALYSIS:

Calculated for $\text{C}_{17}\text{H}_{19}\text{NO.HCl}$: 70.45% C 6.96% H

Found: 70.18% C 7.04% H

Example 32

3-(2-Amino-1-methyl)ethyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine dioxalate

A mixture of 2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine (6.5 g, 21 mmole), 2-chloro-propionamide (4.5 g, 42 mmole), sodium bicarbonate (20 g) 15 and 0.01 g of potassium iodide in DMF (80 ml) was stirred at 85°C for twenty hours. The reaction mixture was cooled and evaporated to a semisolid which was stirred with water and extracted with ether. The ether extracts were washed twice with water, dried (saturated NaCl , anhydrous MgSO_4), 20 filtered and concentrated to an oil (8 g). A solution of the oil (8 g, 21 mmole) in THF (100 ml) was slowly added to a solution of borane in THF (1.01M, 63 mmole), cooled with an ice bath. The solution was 25 stirred at ambient temperature for twenty hours, then at 70°C for two hours. The mixture was cooled, acidified with 3N HCl and refluxed for one hour. The reaction mixture was again cooled, basified with 3N NaOH and extracted with ether. The ether extracts were washed twice with water, dried (saturated NaCl , anhydrous MgSO_4), 30 filtered and concentrated to an oil (7 g), which was converted using the procedure of Example 1 to the dioxalate salt (9 g, 79%, d 80-90°C). This material was recrystallized 35

from an ethyl acetate/ether solution to yield 3-(2-amino-1-methyl)ethyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine dioxalate, d 105°C.

ANALYSIS:

5 Calculated for $C_{20}H_{23}F_3N_2O.2(CO_2H)_2$: 52.94% C 5.00% H
Found: 53.26% C 5.14% H

E x a m p l e 33

1-(p-Methoxyphenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine hydrobromide

10 1-(p-Methoxyphenoxy)-2,3,4,5-tetrahydro-3-benzazepine of Example 30 b (4 g, 15 mmole) was dissolved in 4.5 ml cold 97% formic acid and to this was added 4 ml 37% formaldehyde solution. After stirring at 95°C for four hours, the reaction mixture was cooled, acidified with 30 ml dilute HCl and warmed at 70°C for one hour. The reaction mixture was then cooled, basified with dilute NaOH and extracted with ether. The extracts were washed with water, dried (saturated NaCl, anhydrous $MgSO_4$), filtered and concentrated to an oil (3.7 g, 88%) which was distilled
15 to yield an oil (3.2 g, b.p. 173-175°/70.3 mm). This oil was converted by the addition of ethereal HBr to 1-(p-methoxyphenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine hydrobromide (3.2 g d 205-206°C).

ANALYSIS:

25 Calculated for $C_{18}H_{21}NO_2.HBr$: 59.35% C 6.09% H
Found: 59.21% C 6.06% H

E x a m p l e 34

3-Methyl-1-(p-methylphenoxy)-2,3,4,5-tetrahydro-3-benzazepine Hydrobromide

30 1-(p-Methylphenoxy)-2,3,4,5-tetrahydro-3-benzazepine of Example 29b (1.3 g, 5.1 mole) was dissolved in 4.5 ml cold 97% formic acid and to this was added 4 ml 37% formaldehyde solution. After stirring at 95°C for one hour, the reaction mixture was cooled, acidified with 35 15 ml dilute HCl and warmed at 70°C for 30 minutes. The reaction mixture was then cooled, basified with dilute NaOH and extracted with ether. The organic extracts were

washed with water, dried (saturated NaCl, anhydrous MgSO₄), filtered and concentrated to an oil which was converted by the addition of ethereal HBr to the hydrobromide salt. This material was recrystallized from a 5 20:1 solution of ethyl acetate/methanol to yield 3-methyl-1-(p-methylphenoxy)-2,3,4,5-tetrahydro-3-benzazepine hydrobromide (1.5g, 84%, d 206-207°C).

ANALYSIS:

Calculated for C₁₈H₂₁NO.HBr: 62.07%C 6.37%H
10 Found: 61.62%C 6.40%H

Example 35

7,8-Dimethoxy-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine oxalate

To a solution of 7,8-dimethoxy-1-hydroxy-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (15 g, 15 40 mmole), phenol (3.6 g, 40 mmole) and triphenylphosphine (10.8 g, 41 mmole) in benzene (400 ml), cooled with an ice bath, was slowly dropped a solution of diethyl azo-dicarboxylate (7.2 g, 42 mmole) in benzene (100 ml).
20 After stirring three hours at ambient temperature, the reaction mixture was filtered to remove sym-dicarbethoxy-hydrazine (6.2 g, 94 %, m.p. 132-134°C), then was concentrated to an oil (35 g) which was purified by column chromatography (silica gel, ether) to give 16 g, (88 %) 25 of an oil. A solution of the resultant 7,8-dimethoxy-1-phenoxy-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (15 g, 33 mmole) in toluene (65 ml) was added to a solution of sodium bis (2-methoxyethoxy) aluminum hydride (40 g, 0.2 mole, 70 % in toluene). The 30 reaction mixture was stirred at ambient temperature for two days, then at 70°C for three hours. The reaction mixture was then cooled and poured slowly into 1 liter of dilute NaOH and extracted with ethyl acetate. The organic extracts were washed twice with water, dried (saturated 35 NaCl, anhydrous MgSO₄), filtered and converted utilizing the procedure of Example 1 to the oxalate salt (8 g, 62 %,

m.p. 100°C). This material was recrystallized from a 20:1 solution of ethyl acetate/methanol to give 7,8-dimethoxy-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine oxalate, d 148-149°C.

5 ANALYSIS:

Calculated for $C_{19}H_{23}NO_3 \cdot (CO_2H)_2$: 61.68% C 5.95% H

Found: 61.32% C 5.97% H

E x a m p l e 36

10 7,8-Dimethoxy-3-methyl-1-phenoxy-2,3,4,5-tetrahydro-

3-benzazepine oxalate

To a cooled solution of 7,8-dimethoxy-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine of Example 35b (3.8 g, 13 mmole) and triethylamine (1.5 g, 15 mmole) in chloroform (50 ml) was slowly dropped a solution of ethyl chloroformate (1.6 g, 15 mmole) in chloroform (10 ml). The reaction mixture was stirred twenty hours at ambient temperature, then was concentrated to an oil which was dissolved in ethyl acetate-ether and washed with dilute HCl, water and then dried (saturated NaCl, anhydrous $MgSO_4$). The solution was filtered and concentrated to give 4 g of an oil (85%). A solution of the oil (4 g, 11 mmole) in THF (40 ml) was slowly added to a suspension of $LiAlH_4$ (0.8 g, 22 mmole) in THF (100 ml). After stirring twenty hours at ambient temperature, the reaction mixture was diluted with ether, quenched by slow addition of saturated NH_4Cl and then was filtered. The organic filtrate was washed twice with water, dried (saturated NaCl, anhydrous $MgSO_4$), filtered and concentrated to give 3.1 g of an oil. This oil was purified by column chromatography (silica gel, THF) to give 2.3 g of an oil (67%). This oil was converted using the procedure of Example 1 to the oxalate salt and recrystallized from a 20:1 solution of ethyl acetate/methanol to give 1.8 g of a solid, m.p. 160°C. This material was again recrystallized from a 20:1 solution of ethyl acetate/methanol to give 1.5 g of 7,8-dimethoxy-3-methyl-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine oxalate, d 169-170°C.

ANALYSIS:

Calculated for $C_9H_{23}NO_3 \cdot (CO_2H)_2$: 62.52% C 6.25% H

Found: 62.18% C 6.15% H

Example 37

5 7,8-Dimethoxy-3-ethyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine hydrochloride

To a solution of 7,8-dimethoxy-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine (5.5 g, 15 mmole), the compound of Example 19, and triethylamine (1.8 g, 18 mmole) in chloroform (70 ml), cooled with an ice bath, is slowly added a solution of acetyl chloride (1.4 g, 18 mmole) in chloroform (30 ml). After one hour, the mixture was concentrated to a semi-solid which was stirred with water and extracted with ethyl acetate-ether.

10 The organic extracts were washed with dilute HCl, water then dried (saturated NaCl, anhydrous $MgSO_4$). The solution was filtered and concentrated to an oil (5 g, 82%). A solution of the oil (5 g, 12 mmole) in THF (40 ml) was slowly added to a suspension of $LiAlH_4$ (0.9 g, 24 mmole)

15 in THF (100 ml), cooled with an ice bath. After one hour the mixture was quenched by slow addition of saturated NH_4Cl , then was filtered. The filtrate was washed twice with water, dried (saturated NaCl, anhydrous $MgSO_4$), filtered and concentrated to give 5 g of an oil which was purified by column chromatography (silica gel, THF) to give 3.9 g of an oil. This material was converted by the addition of ethereal HCl to the hydrochloride salt and recrystallized from a 20:1 solution of ethyl acetate/methanol to give 3 g (57%) of a solid, d 180-185°C. This

20 material was again recrystallized to give 7,8-dimethoxy-3-ethyl-2,3,4,5-tetrahydro-1-(p-trifluoromethylphenoxy)-3-benzazepine hydrochloride, d 185-185°C.

25

30

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ANALYSIS:

Calculated for $C_{21}H_{24}F_3NO_3 \cdot HCl$: 58.40% C 5.84% H

Found: 58.10% C 5.80% H

Example 38

7,8-Dimethoxy-1-(4-methoxyphenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine hydrochloride

To a solution of 7,8-dimethoxy-1-hydroxy-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (27 g, 72 mmole), p-methoxyphenol (9 g, 72 mmole) and triphenylphosphine (23 g, 86 mmole) in benzene (300 ml), cooled with an ice bath, was slowly dropped a solution of diethyl azodicarboxylate (15 g, 86 mmole) in benzene (100 ml).

After stirring twenty hours at ambient temperature, the reaction mixture was filtered to remove sym-dicarbethoxyhydrazine (11.4 g, 90 %, m.p. 132-4°C) then concentrated to an oil (65 g) which was purified by column chromatography (silica gel, dichloromethane) to give 27 g (78%) of an oil. The resulting 7,8-dimethoxy-1-(4-methoxyphenoxy)-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (17 g, 35 mmole) in toluene (30 ml) was added to a solution of sodium bis (2-methoxyethoxy)aluminum hydride (70 g, 0.35 mole, 70% in toluene). The reaction mixture was stirred at ambient temperature for three days, then was diluted with toluene and quenched by slow addition of 10 % NaOH. The mixture was filtered and the organic filtrate was washed twice with water, dried (saturated NaCl, anhydrous $MgSO_4$), filtered and concentrated to an oil which was converted to the oxalate salt, as by the procedure of Example 1, then immediately rebasified to give 7 g, (60 %) of an oil. The resulting 7,8-dimethoxy-1-(4-methoxyphenoxy)-2,3,4,5-tetrahydro-3-benzazepine (7 g, 21 mmole) was dissolved in 9 ml cold 88 % formic acid and to this was added 8 ml 33 % formaldehyde solution. The mixture stirred at 90°C for two hours, then was cooled, diluted with water and basified with sodium carbonate. The oil which separated was extracted with ethyl acetate-ether then was washed twice with water, dried (saturated NaCl, anhydrous $MgSO_4$), filtered and concentrated to an oil which was converted to the hydrochloride salt (6.7 g, 84 %, m.p. 130-140°C). This material was

recrystallized from a 20:1 solution of ethyl acetate/methanol to give 7,8-dimethoxy-1-(4-methoxyphenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine hydrochloride, (4.1 g, m.p. 197-198°C).

5 ANALYSIS:

Calculated for $C_{20}H_{25}NO_4 \cdot HCl$: 63.23% C 6.90% H
Found: 63.20% C 6.89% H

E x a m p l e 39

3-(p-Toluenesulfonyl)-1-(4-trifluoromethylphenoxy)-

10 2,3,4,5-tetrahydro-3-benzazepine

A solution of 1-hydroxy-3-(p-toluenesulfonyl)-2,3,4,5-tetrahydro-3-benzazepine (28.56 g, 0.09 mole) and dry DMF (180 ml) was added dropwise at room temperature under nitrogen to a vigorously stirred suspension of NaH (4.85 g, 50 % of 98% in oil, 0.099 mole, washed twice with hexane) in DMF (135 ml). After the addition was completed, the mixture was warmed briefly to 60°C, then cooled to room temperature. To this mixture was added rapidly dropwise a solution of p-fluorobenzotrifluoride (15.51 g, 0.0945 mole) in DMF (90 ml). After stirring at room temperature for 24 hours the reaction mixture was warmed briefly to 55°C, then allowed to cool slowly to room temperature. This mixture was poured into water (3 l.) and extracted with methylene dichloride. The methylene dichloride solution was washed twice with water, saturated sodium chloride, treated with charcoal and filtered through Celite to give a colored solution. The aqueous portion was extracted several more times with ether, and this ether extract treated similarly to the methylene dichloride extract. The combined extracts yielded 38 g, of an oil (91.5 %) which was chromatographed on 500 g of silica gel and eluted with methylene dichloride to yield 23.81 g (57 %) of product, which crystallized from ether to yield 3-(p-toluenesulfonyl)-1-(4-trifluoromethylphenoxy)-2,3,4,5-tetrahydro-3-benzazepine product, m.p. 114-115°C. Recrystallization from hexane gave product, m.p. 115-117°C.

ANALYSIS:

Calculated for $C_{24}H_{22}F_3NO_3S$: 62.45% C 4.81% H 3.03% N
Found: 62.29% C 4.81% H 2.94% N

It is predicted that if the resultant 3-p-toluene-
5 sulfonyl-1-(4-trifluoromethylphenoxy)-2,3,4,5-tetrahydro-
3-benzazepine of Example 39 is reacted with sodium bis
(2-methoxyethoxy)aluminum hydride, and then methylated in
the manner described in Example 38, that the compound of
the invention, 1-(4-trifluoromethylphenoxy)-3-methyl-
10 2,3,4,5-tetrahydro-3-benzazepine will be obtained.

Example 40

1-(4-Chlorophenoxy)-3-(p-toluenesulfonyl)-2,3,4,5-tetrahydro-3-benzazepine

A solution of 1-hydroxy-3-(p-toluenesulfonyl)-
15 2,3,4,5-tetrahydro-3-benzazepine (5.8 g, 18.27 mmole) in
DMF (40 ml) was added at room temperature to a suspension
of sodium hydride (1 g of 50 % oil dispersion, 20.098 mmol)
(washed twice with hexane) in DMF (25 ml). After stirring
fifteen minutes at room temperature the mixture was
20 warmed briefly to 80°C, cooled to 65°C, then a solution
of p-chlorofluorobenzene (2.5 g, 19.18 mmol) in DMF (25 ml)
was added. After three days at room temperature, the
temperature was raised to 80°C for 24 hours. After an
additional 24 hours at 100-120°C an additional 0.5 g of
25 99 % NaH and 1 g of p-chlorofluorobenzene was added,
and heating continued for 12 hours. Most of the DMF was
removed under vacuum, the residue was poured onto ice and
extracted with ether. The ether solution was dried and the
ether removed to give 6.1 g of an oil (78 %). The oil was
30 dissolved in ether-hexane and on standing gave 2 g of a
solid (25.6 %). Trituration with methanol gave 1.5 g of a
solid (19 %). Recrystallization from methanol gave 1.17 g
of a solid, m.p. 110-112°C. This solid was again dissolved
35 in hot methanol, cooled to room temperature and filtered
through Celite. From the filtrate crystallized 0.83 g
of 1-(4-chlorophenoxy)-3-(p-toluenesulfonyl)-2,3,4,5-
tetrahydro-3-benzazepine, m.p. 116-118°C (11 %).

ANALYSIS:

Calculated for $C_{23}H_{22}ClNO_3S$: 64.54% C 5.19% H 3.27% N
Found: 64.60% C 5.20% H 3.11% N

It is predicted that if the resultant 1-(4-chlorophenoxy)-3-(p-toluenesulfonyl)-2,3,4,5-tetrahydro-3-benzazepine of Example 40 is reacted with sodium bis(2-methoxyethoxy)-aluminum hydride and then methylated in the manner described in Example 38, that the compound 1-(4-chlorophenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine will be obtained.

Example 41

3-(p-Toluenesulfonyl)-1-(3-trifluoromethylphenoxy)-2,3,4,5-tetrahydro-3-benzazepine

A solution of 1-hydroxy-3-(p-toluenesulfonyl)-2,3,4,5-tetrahydro-3-benzazepine (7.14 g, 0.0225 mole) in DMF (45 ml) was added dropwise at room temperature to a suspension of sodium hydride (1.21 g of 50 % oil dispersion, 98 %), previously washed twice with hexane, in DMF (35 ml). The mixture was stirred at room temperature of 1/2 hour, then warmed briefly to 70°C and slowly cooled to room temperature. A solution of m-fluorobenzotrifluoride (3.9 g) in DMF (25 ml) was added rapidly dropwise, and the mixture stirred at room temperature for two days. The reaction mixture was heated overnight, about 16 hours, at 65-70°C. An additional 0.5 g of 99 % NaH and 1g of m-fluorobenzotrifluoride was added, and the mixture heated at 100°C for about 4 hours. The mixture was cooled to room temperature, diluted with benzene, then most of the solvent was removed under vacuum. The residue was poured onto ice and extracted with ether. The ether solution was washed with water and dried and the solvent removed to give 7.5 g of an oil (72 %). This was dissolved in ether and hexane and allowed to stand at room temperature to give 6.3 g (61 %) of a solid, m.p. 105-111°C. Recrystallization from methanol gave 4.64 g of crystalline material with the same melting point. A final product was obtained by chromatographing 4.15 g on silica gel (90 g) with methylene dichloride,

and crystallizing the product from ether-petroleum ether to give 3.94 g of 3-(p-toluenesulfonyl)-1-(3-trifluoromethylphenoxy)-2,3,4,5-tetrahydro-3-benzazepine, m.p. 112-113.5°C (40 % yield).

5 ANALYSIS:

Calculated for $C_{24}H_{22}F_3NO_3S$: 62.45% C 4.81% H 3.03% N

Found: 62.11% C 4.97% H 2.91% N

It is predicted that if the 3-(p-toluenesulfonyl)-1-(3-trifluoromethylphenoxy)-2,3,4,5-tetrahydro-3-benzazepine of Example 41 is reacted with sodium bis (2-methoxyethoxy) aluminum hydride and then methylated, in the manner described in Example 38, that the compound 3-methyl-1-(3-trifluoromethylphenoxy)-2,3,4,5-tetrahydro-3-benzazepine will be obtained.

15 Example 42

7,8-Dimethoxy-1-(4-fluorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine maleate

To a solution of 7,8-dimethoxy-1-hydroxy-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (10 g, 26 mmole), 4-fluorophenol (3 g, 26 mmole) in 200 ml benzene, cooled with an ice bath, was slowly dropped a solution of diethyl azodicarboxylate (4.8 g, 28 mmole) in 60 ml benzene. After stirring two days at ambient temperature, the reaction mixture was filtered to remove sym-dicarbethoxyhydrazine (4 g, 86 %, mp 132-134°C), then evaporated to 24 g of an oil which was purified by high pressure liquid chromatography (HPLC), (silica gel, dichloromethane) to give 9 g (71 %) of a viscous oil. A solution of 7,8-dimethoxy-1-(4-fluorophenoxy)-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (9 g, 19 mmole) in sodium bis (2-methoxyethoxy) aluminum hydride (3.4 M in toluene, 100 ml, 0.4 mole) was stirred two days at ambient temperature, then was diluted with ether and quenched by slow addition of 3N NaOH. The organic phase was washed with water and saturated NaCl and was dried (anhydrous $MgSO_4$) filtered and evaporated to an oil which was converted to

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the maleate salt by the addition of ethereal maleic acid (4.2 g, 51 %, mp 155-158°C). This material was recrystallized twice from isopropanol to yield 2.6 g of 7,8-dimethoxy-1-(4-fluorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine maleate d 168-169°C.

Calculated for $C_{18}H_{20}FNO_3 \cdot C_4H_4O_4$: 60.96% C 5.58% H 3.23% N
Found: 60.99% C 5.58% H 3.21% N

E x a m p l e 43

7,8-Dimethoxy-1-(4-fluorophenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine maleate

7,8-Dimethoxy-1-(4-fluorophenoxy)-2,3,4,5-tetrahydro-3-benzazepine (3.5 g, 11 m mole) of Example 42 was dissolved in 9 ml 95 % formic acid and to this was added 8 ml 37 % formaldehyde solution. The mixture was stirred at 75°C for one hour, then was cooled, diluted with water and basified with sodium carbonate. The oil which separated was extracted with ether then was washed with water, dried (saturated NaCl, anhydrous $MgSO_4$), filtered and evaporated to an oil. The oil was converted as in Example 42 to the maleate salt (3.7 g, mp 125-135°C). This material was recrystallized twice from isopropanol to yield 2.7 g (55 %) of 7,8-dimethoxy-1-(4-fluorophenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine maleate d 152-153°C.

Calculated for $C_{19}H_{22}FNO_3 \cdot C_4H_4O_4$: 61.73% C 5.86% H 3.13% N
Found: 61.69% C 5.90% H 3.11% N

E x a m p l e 44

7,8-Dimethoxy-3-ethyl-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine maleate

To a solution of 7,8-dimethoxy-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine (3 g, 10 m mole) and triethylamine (1.2 g, 12 m mole) in 100 ml chloroform was added a solution of acetyl chloride (0.9 g, 12 m mole) in 20 ml chloroform. After one hour, the mixture was evaporated, stirred with water and extracted into ether. The organic extracts were washed with water, saturated NaCl and were dried, filtered and evaporated to 4 g of a viscous oil. A solution

of 3-acetyl-7,8-dimethoxy-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine (3.4 g, 10 mmole) in 125 ml tetrahydrofuran was slowly dropped into a stirring suspension of LiAlH₄ (1 g, 26 mmole) in 100 ml THF. After stirring two hours at ambient temperature the reaction mixture was diluted with ether, then quenched by slow addition of saturated ammonium chloride. After filtering, the organic phase was washed with water, saturated NaCl and was dried (anhydrous MgSO₄), filtered and evaporated to 3.4 g of an oil. This oil was purified by column chromatography (silica gel, tetrahydrofuran) to give 2 g of an oil. This oil was converted to the maleate salt by the addition of ethereal-maleic acid and recrystallized from isopropanol/ether to give 2 g (45 %) of 7,8-dimethoxy-3-ethyl-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine maleate, mp 129-130°C.

ANALYSIS:

Calculated for C₂₀H₂₅NO₃·C₄H₄O₄: 64.99%C 6.59%H 3.16%N
Found: 65.24%C 6.58%H 3.05%N

E x a m p l e 45

20 1-(4-Chlorophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine maleate

To a solution of 7,8-dimethoxy-1-hydroxy-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (20 g, 53 mmole), 4-chlorophenol (6.8 g, 53 mmole) and triphenyl-phosphine (14.6 g, 56 mmole) in 400 ml benzene, cooled with an ice bath, was slowly dropped a solution of diethyl azodicarboxylate (9.7 g, 56 mmole) in 120 ml benzene. After stirring twenty hours at ambient temperature, the reaction mixture was filtered to remove sym-dicarbethoxy-hydrazine (8 g, 86 %, m.p. 131-132°C), then evaporated to yield 48 g of an oil which was purified by HPLC (silica gel, dichloromethane) to give 20 g (78 %) of an oil. A solution of 1-(4-chlorophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-(p-toluenesulfonyl)-3-benzazepine (20 g, 41 mmole) in sodium aluminum bis (2-methoxyethoxy) hydride (3.4 M in toluene, 200 ml, 0.8 mole) was stirred 2.5 days

at ambient temperature, then was diluted with anhydrous ether and was quenched by slow addition of 3N NaOH. The organic phase was washed with water and saturated NaCl and was dried (anhydrous $MgSO_4$), filtered and evaporated to yield 16 g of an oil which was converted to the maleate salt, then immediately was rebasified to give 6.5 g (47 %) of an oil. The oil was purified by HPLC (silica gel, 1 % diethylamine/ ethylacetate) to give 4.4 g of an oil, of which 2.3 g was converted to the maleate salt as in Example 42, then recrystallized from isopropanol/ether to give 2.2 g of 1-(4-chlorophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine maleate, d 135-137°C.

ANALYSIS:
Calculated for $C_{18}H_{20}ClNO_3 \cdot C_4H_4O_4$: 58.73%C 5.38%H 3.11%N
15 Found: 58.61%C 5.32%H 3.02%N

Example 46

1-(4-Chlorophenoxy)-7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-3-benzazepine maleate
1-(4-Chlorophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine (3 g, 6 mmole) was dissolved in 9 ml 95 % formic acid and to this was added 8 ml 37 % formaldehyde solution. The mixture was stirred at 75°C for one hour, then was cooled, diluted with water and basified with sodium carbonate. The oil which separated was extracted with ether, washed with water, saturated NaCl, was dried (anhydrous $MgSO_4$), filtered and evaporated to 2.1 g of an oil. This oil was converted to the maleate salt and recrystallized from isopropanol-ether to give 1.9 g (68 %) of 1-(4-chlorophenoxy)-7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-3-benzazepine maleate, d 154-154°C.

ANALYSIS:
Calculated for $C_{19}H_{22}ClNO_3 \cdot C_4H_4O_4$: 59.54%C 5.65%H 3.02%N
Found: 59.93%C 5.74%H 2.91%N

Example 47

7,8-Dimethoxy-3-[4,4-bis-(p-fluorophenyl)butyl]-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine oxalate
A mixture of 7,8-dimethoxy-1-phenoxy-2,3,4,5-tetrahydro-

3-benzazepine of Example 35 (2.6 g, 8.7 mmole), 4,4-bis-(p-fluorophenyl)-butyl chloride (2.9 g, 10.4 mmole), potassium carbonate (3 g, 22 mmole) and 0.01 g potassium iodide in 90 ml dimethyl formamide was stirred twenty hours at 80°C. The reaction mixture was cooled and concentrated to an oil that was stirred with water and extracted with ether. The organic extracts were washed with water and saturated NaCl, and were dried (anhydrous MgSO₄), filtered and evaporated to 6 g of an oil. This oil was purified by column chromatography (alumina, ether) to give 5 g of an oil, then by high pressure liquid chromatography (silica gel, 5 % ethyl acetate/dichloromethane) to give 2.3 g of a light oil. This oil was converted to the oxalate salt as in Example 1 and recrystallized from isopropanol/ether to give 1.8 g (33 %) of 7,8-dimethoxy-3-4,4-bis-(p-fluorophenyl)-butyl-7-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine oxalate, d 114-116°C.

ANALYSIS:

Calculated for C₃₄H₃₅F₂NO₃·(CO₂H)₂: 68.23% C 5.89% H 2.21% N
Found: 68.32% C 5.93% H 2.24% N

E x a m p l e 48

1-(4-Bromophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine maleate

A solution of 7,8-dimethoxy-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine of Example 35 (6.5 g, 22 mmole) in 300 ml methanol was acidified to pH 1 with ethereal hydrogen chloride. After this solution was cooled with an ice bath, N-bromosuccinimide (4.2 g, 24 mmole) was added. The reaction mixture slowly warmed to ambient temperature, was evaporated, stirred with water, basified with saturated sodium carbonate and was extracted with ethyl acetate-ether. The organic extracts were washed with water, saturated sodium chloride and were dried (anhydrous MgSO₄), filtered and evaporated to 8 g of any oil. This oil was converted to the maleate salt (8 g, 74 %, m.p. 95-100°C) by the

addition of ethereal maleic acid of which 4 g was recrystallized twice from isopropanol-ether to give 2.4 g (45 %) of 1-(4-bromophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine maleate, d 145-146°C.

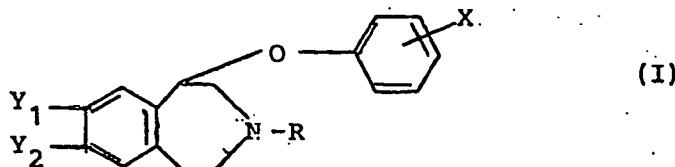
5 ANALYSIS:

Calculated for $C_{18}H_{20}BrNO_3 \cdot C_4H_4O_4$: 53.45%C 4.89%H 2.83%N
Found: 53.58%C 4.95%H 2.83%N

Claims:

1. A compound having the formula

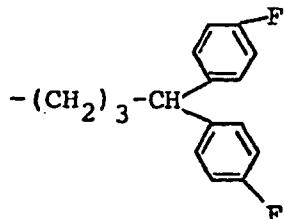
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wherein Y_1 and Y_2 are the same or different and are hydrogen or lower alkoxy; X is hydrogen, halogen, lower alkyl, lower alkoxy, CF_3 , NO_2 , CN and NH_2 ; R is hydrogen, lower alkyl, cycloalkyl lower alkyl,

15



20

aryl lower alkyl of the formula -alkylene-, where Z is hydrogen, lower alkyl, lower alkoxy, CF_3 , NO_2 or NH_2 ; or an alkylene amine of the formula -alkylene- $N_{R_1}_{R_2}$, where R_1 and R_2 are the same or different and are hydrogen or lower alkyl; and the pharmaceutically acceptable acid addition salts thereof.

25

2. The compound as defined in Claim 1 wherein R is hydrogen.

3. The compound as defined in claim 1 wherein R is lower alkyl.

30

4. The compound as defined in claim 1 which is 3-(2-aminoethyl)-2,3,4,5-tetrahydro-1-(4-trifluoromethylphenoxy)-3-benzazepine or a pharmaceutically acceptable salt thereof.

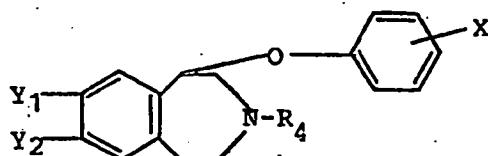
5. The compound as defined in claim 1 which is 7,8-dimethoxy-2,3,4,5-tetrahydro-1-(4-trifluoromethylphenoxy)-3-benzazepine or a pharmaceutically acceptable salt thereof.
10. The compound as defined in claim 1 which is 1-(3-chlorophenoxy)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepine or a pharmaceutically acceptable salt thereof.
15. The compound as defined in claim 1 which is 1-(4-methoxyphenoxy)-2,3,4,5-tetrahydro-3-benzazepine or a pharmaceutically acceptable salt thereof.
20. The compound as defined in claim 1 which is 3-(2-amino-1-methyl)ethyl-2,3,4,5-tetrahydro-1-(4-trifluoromethylphenoxy)-3-benzazepine or a pharmaceutically acceptable salt thereof.
25. The compound as defined in claim 1 which is 7,8-dimethoxy-3-methyl-1-phenoxy-2,3,4,5-tetrahydro-3-benzazepine or a pharmaceutically acceptable salt thereof.
30. The compound as defined in claim 1 which is 7,8-dimethoxy-1-(4-methoxyphenoxy)-3-methyl-2,3,4,5-tetrahydro-3-benzazepine or a pharmaceutically acceptable salt thereof.
35. The compound as defined in claim 1 which is 3-(3-amino-propyl)-2,3,4,5-tetrahydro-1-(4-trifluoromethylphenoxy)-3-benzazepine or a pharmaceutically acceptable salt thereof.

13. The compound as defined in claim 1 which is 7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-1-(4-trifluoromethylphenoxy)-3-benzazepine or a pharmaceutically acceptable salt thereof.

5

14. A compound of the formula

10



15 alkoxy carbonyl; cyano, lower alkyl; acyl of the formula

where Y_1 and Y_2 are the same or different and are hydrogen or lower alkoxy; X is hydrogen, halogen, lower alkyl,

lower alkoxy, CF_3 , CN , NO_2 and NH_2 ; R_1 is lower

15 alkoxy carbonyl; cyano; lower alkyl; acyl of the formula

8

R_5^C where R_5 is lower alkyl, lower alkoxy, carbamoyl-lower alkyl of the formula R_7O
 $-lower\text{-alkylene-N-C-O-R}_6$,

30

where R_6 is lower alkyl, and R_7 is H or lower alkyl; an lower alkyl of the formula

At lower alkyl of the formula

25

-alkylene-

phenyl of the formula ; and phenyl sulfonyl of the formula 

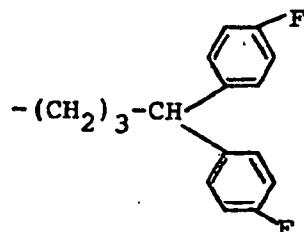
25 the formula 

where Z is hydrogen, lower alkyl, lower alkoxy, halogen, CF_3 , NO_2 and NH_2 .

30 15. A process for preparing a compound of the formula I

wherein Y_1 and Y_2 are the same or different and are hydrogen or lower alkoxy; X is hydrogen, halogen, lower alkyl, lower alkoxy, CF_3 , CN , NO_2 or NH_2 ; R is hydrogen, lower alkyl, cycloalkyl, lower alkyl,

5



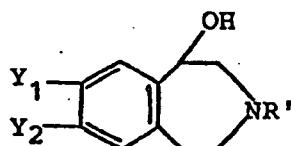
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aryl lower alkyl of the formula -alkylene- , where Z is hydrogen, halogen lower alkyl, lower alkoxy, CF_3 , NO_2 and NH_2 ; or an alkylene amine of the formula -alkylene- N _{R_1} R_2 where R_1 and R_2 are the same or different and are hydrogen or lower alkyl, and the alkylene moiety is of 1 to 6 carbon atoms and the pharmaceutically acceptable acid addition salts thereof, which comprises

15

20

a) reacting a compound of the formula



III/IV

25

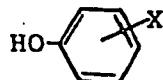
wherein Y_1 and Y_2 are as previously defined and R' is hydrogen, the tosyl or the mesyl group, with a halide having the formula

30



V

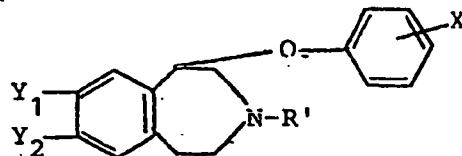
where X is as previously defined or with a phenol of the formula



VIII

5

where X is as previously defined, to form a compound of the formula



VI/VII

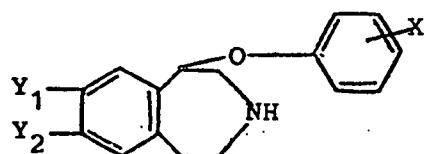
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where X, Y₁ and Y₂ are as previously defined and R' is hydrogen, or the tosyl or mesyl group, and reducing the compound obtained wherein R' is the tosyl or mesyl group with an alkali metal or with a complex boron or aluminum hydride to form a compound of the above formula wherein R' is hydrogen, and

15

b) optionally reacting a compound of the formula VI

20

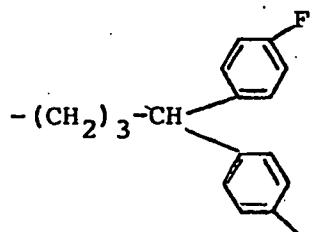


VI

25

wherein X, Y₁ and Y₂ are as previously defined, under conventional nucleophilic reaction conditions with a halide of the formula Hal-R₃ where Hal is halogen and R₃ is lower alkyl, cycloalkyl lower-alkyl, a group of the formula

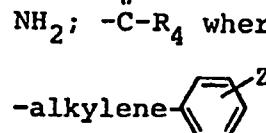
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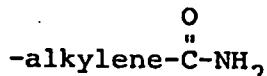
alkylene- where the alkylene moiety is of 1 to 6 carbon atoms and Z is hydrogen, halogen, lower alkyl,

lower alkoxy, CF_3 , NO_2 or NH_2 ; $-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-\text{R}_4$ where R_4 is alkyl of 1 to 5 carbon atoms or



where the alkylene moiety is of 1 to 5 carbon atoms

5 and Z is as defined above; $-\text{alkylene}-\text{CN}$ where the alkylene moiety is of 1 to 5 carbon atoms; $-\text{alkylene}-\text{N}(\text{R}_1)\text{R}_2$ where the alkylene moiety is of 1 to 6 carbon atoms and R_1 and R_2 are the same or different and are hydrogen and lower alkyl, or R_3 is



10 where the alkylene moiety is of 1 to 5 carbon atoms, to form a compound of the formula I wherein R is as defined for R_3 above, and

15 c) optionally reducing a compound of the formula I wherein

R is O



to form a compound of the formula I wherein R is lower alkyl or aryl lower alkyl

20

d) optionally reducing a compound of the formula I wherein

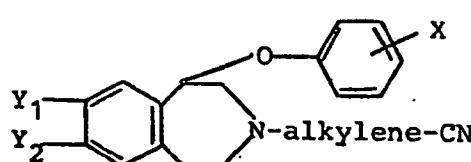
R is O



to form a compound of the formula I wherein R is methyl,

25

e) optionally reacting a compound of the formula VI with a branched or straight chained alkenyl cyanide having the formula $-\text{alkenyl}-\text{CN}$ where the alkenyl moiety is 1 to 5 carbon atoms to form an intermediate compound of the formula



XIV

wherein X , Y_1 and Y_2 are as previously defined, and the alkylene moiety is as previously defined,

- f) optionally reducing a compound of the formula XIV
5 to form a compound of the formula I wherein R is
-alkylene- CH_2-NH_2 where the alkylene moiety is of 1 to
5 carbon atoms,
- g) optionally reacting a compound of the formula I wherein
10 R is -alkylene- $N^R₁_R²$ where the alkylene moiety is of
1 to 6 carbon atoms and at least R_1 is hydrogen, with
a lower alkyl halide to form at least a mono substituted
N-alkyl derivative thereof, or with an alkyl halo-
formate followed by reducing the resultant compound
15 to form at least a monosubstituted N-methyl derivative,
and
- h) optionally preparing in a conventional manner the
pharmaceutically acceptable acid addition salts thereof.

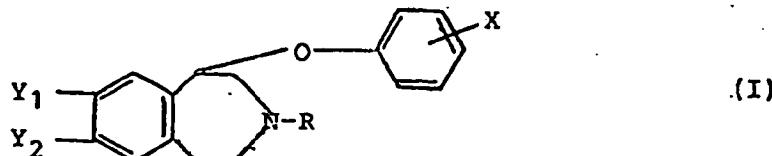
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16. Process for the preparation of a pharmaceutical composition, characterised in that a compound of the formula I and/or one of its pharmaceutically acceptable acid addition salts is brought, together with at least one solid, liquid or 25 semi-liquid excipient or auxiliary and, optionally, together with a further active ingredient, into a suitable dosage form.
- 30 17. A pharmaceutical composition containing a compound of the formula I as claimed in claim 1 and/or one of its pharmaceutically acceptable acid addition salts.
- 35 18. A compound of the formula I or one of its pharmaceutically acceptable acid addition salts as claimed in claim 1 for use as medicament.

Claims for Austria:

1. A process for preparing a compound of the formula I

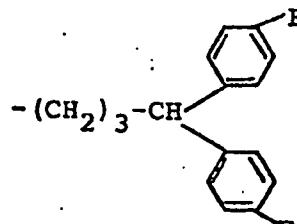
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wherein Y_1 and Y_2 are the same or different and are hydrogen or lower alkoxy; X is hydrogen, halogen, lower alkyl, lower alkoxy, CF_3 , CN , NO_2 and NH_2 ; R is hydrogen, lower alkyl, cycloalkyl, lower alkyl,

15



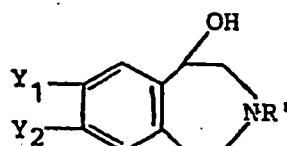
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aryl lower alkyl of the formula -alkylene-
where Z is hydrogen, halogen, lower alkyl, lower alkoxy, CF_3 , NO_2 or NH_2 ; or an alkylene amine of the formula -alkylene-N_{R1}^{R2} where R_1 and R_2 are the same or different and are hydrogen or lower alkyl, and the alkylene moiety is of 1 to 6 carbon atoms and the pharmaceutically acceptable acid addition salts thereof, which comprises.

25

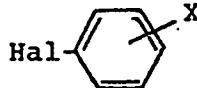
a) reacting a compound of the formula

30



wherein Y_1 and Y_2 are as previously defined and R' is hydrogen, the tosyl or the mesyl group with a halide having the formula

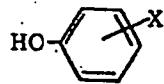
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V

where X is as previously defined or with a phenol of the formula

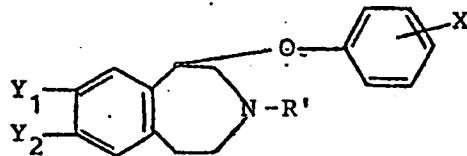
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VIII

where X is as previously defined, to form a compound of the formula

15



VI/VII

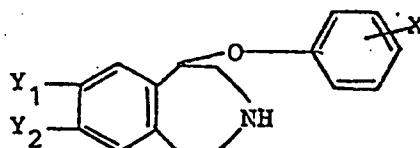
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where X , Y_1 and Y_2 are as previously defined and R' is hydrogen, or the tosyl or mesyl group, and reducing the compound obtained wherein R' is the tosyl or mesyl group with an alkali metal or with a complex boron or aluminum hydride to form a compound of the above formula wherein R' is hydrogen, and

25

b) optionally reacting a compound of the formula VI

30

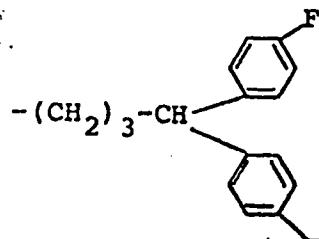


VI

wherein X , Y_1 and Y_2 are as previously defined, under conventional nucleophilic reaction conditions with a halide of the formula $\text{Hal}-R_3$ where Hal is halogen and

R_3 is lower alkyl, cycloalkyl lower-alkyl, a group of the formula

5



10

alkylene- where the alkylene moiety is of 1 to 6 carbon atoms and Z is hydrogen, halogen, lower alkyl,

15

lower alkoxy, CF_3 , NO_2 or NH_2 ; $-\overset{O}{C}-R_4$ where R_4 is alkyl of 1 to 5 carbon atoms or

20

-alkylene-

where the alkylene moiety is of 1 to 5 carbon atoms

and Z is as defined above; -alkylene-CN where the

alkylene moiety is of 1 to 5 carbon atoms; -alkylene- $N\overset{R_1}{\underset{R_2}{\overset{O}{C}}}$ where the alkylene moiety is of 1 to 6 carbon atoms and R_1 and R_2 are the same or different and are hydrogen and lower alkyl, or R_3 is

-alkylene- $C\overset{O}{\underset{N\overset{R_2}{H_2}}{C}}$

where the alkylene moiety is of 1 to 5 carbon atoms, to form a compound of the formula I, wherein R is as defined for R_3 above, and

25 c) optionally reducing a compound of the formula I wherein

R is O

$-\overset{O}{C}-R_4$

to form a compound of the formula I wherein R is lower alkyl or aryl lower alkyl

30

d) optionally reducing a compound of the formula I wherein

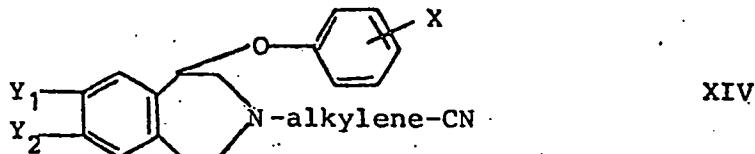
R is O

$-\overset{O}{C}-O$ -lower alkyl

to form a compound of the formula I wherein R is methyl,

0096838

e) optionally reacting a compound of the formula VI with a branched or straight chained alkenyl cyanide having the formula -alkenyl-CN where the alkenyl moiety is 1 to 5 carbon atoms to form an intermediate compound of the formula



10

wherein X, Y₁ and Y₂ are as previously defined, and the alkylene moiety is as previously defined,

15 f) optionally reducing a compound of the formula XIV
 to form a compound of the formula I wherein R is
 -alkylene- $\text{CH}_2\text{-NH}_2$ where the alkylene moiety is of 1 to
 5 carbon atoms,

20 g) optionally reacting a compound of the formula I wherein
 R is -alkylene- $\text{N}^{\text{R}_1}_{\text{R}_2}$ where the alkylene moiety is of
 1 to 6 carbon atoms and at least R_1 is hydrogen, with
 a lower alkyl halide to form at least a mono substituted
 N-alkyl derivative thereof, or with an alkyl halo-
 formate followed by reducing the resultant compound
 25 to form at least a monosubstituted N-methyl derivative,

30

2. Process for the preparation of a pharmaceutical composition, characterised in that a compound of the formula I and/or one of its physiologically acceptable acid addition salts is brought, together with at least one solid, liquid or semi-liquid excipient or auxiliary and, optionally, together with a further active ingredient, into a suitable dosage form.



DOCUMENTS CONSIDERED TO BE RELEVANT			EP 83105610.6
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. *)
A	<u>EP - A1 - 0 002 327 (SMITHKLINE)</u> * Claims 1,15; examples 12,13 --	1,15,16, 17,18	C 07 D 223/16 A 61 K 31/55
A	<u>GB - B - 1 118 688 (SCHERICO)</u> * Claims 1,17; page 1, lines 28-50 *	1,15,17, 18	
A	<u>DE - A1 - 2 640 831 (SHIONOGI)</u> * Claims 1,6,7; page 4 *	1,15,17, 18	
A	<u>DE - B2 - 2 166 866 (SUMITOMO)</u> * Claims; column 4, lines 21-23 *	1,15,16 17,18	
			TECHNICAL FIELDS SEARCHED (Int. Cl. *)
			C 07 D 223/00 C 07 D 243/00
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
VIENNA	24-08-1983	LUX	
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